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DEVELOPMENT OF ABUSE DETERRENT FORMULATIONS USING
HOT MELT EXTRUSION

A thesis submitted in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

to the faculty of

DEPARTMENT OF GRADUATE DIVISION

of

COLLEGE OF PHARMACY AND HEALTH SCIENCES

at

ST. JOHN'S UNIVERSITY

New York

by

PAVAN KUMAR NUKALA

Date Submitted:

Date Approved:

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ABSTRACT

DEVELOPMENT OF ABUSE DETERRENT FORMULATIONS USING HOT MELT EXTRUSION

PAVAN KUMAR NUKALA

In recent years prescription drug diversion, misuse, abuse represent a growing problem for the United States. Oral ingestion, snorting, injection are most commonly employed routes of abuse. To circumvent this problem hot melt extrusion (HME) was employed to prepare abuse deterrent formulation (ADF).

Abuse Deterrent Immediate Release Egg-Shaped Tablet Using 3D Printing Technology: Quality by Design to Optimize Drug Release and Extraction.

In current work, we developed egg-shaped tablet (egglet) using fused deposition modeling (FDM) 3D printing. Drug-loaded polymeric filaments (1.5 mm) were prepared using HME followed by printing into egglets of different sizes and infill densities. Based on printability, crush resistance polyvinyl alcohol (PVA) was used further. Later, egglets were evaluated for abuse deterrence properties based on USFDA guidance. A multifactorial design was used to optimize solvent extraction, drug release. Extreme hardness (> 500 N), large particle size (> 1 mm) on mechanical manipulation

established snorting deterring property while $<20\%$ drug extraction in 5 min ($\% S_{\text{ext}}$) demonstrated deterrence for injection abuse. Quality target product profile $D_{85} < 30$ min, $\% S_{\text{ext}} < 20$ was achieved with egglets of 6 mm diameter, 45% infill density, 15% w/w drug loading.

Development of Multi-dose Oral Abuse Deterrent Formulation of Loperamide Using Hot melt extrusion.

Loperamide, an over the counter anti-diarrheal drug, also referred as "poor man's methadone". Abusers consume more than 30 tablets to achieve euphoria and to combat opioid withdrawal. But supratherapeutic doses causes respiratory depression, cardiac dysrhythmia, mortality. Aim is designing a tablet which can immediate release loperamide in diarrheic patients (single tablet) while stops release in case of intentional multi-dose ingestion. Loperamide was molecularly dispersed into gastric soluble cationic polymers - Eudragit[®] EPO, Kollicoat[®] Smartseal 100P using HME to obtain filament. Filaments were milled and compressed into tablets ((Eudragit[®] EPO (SJU1) and Kollicoat[®] Smartseal (SJU2)) with optimized amount of L-arginine. Dissolution in 250 mL of Fasted state simulated gastric fluid (FaSSGF) revealed that single tablet of Imodium[®] (marketed formulation) and SJU1 showed $>85\%$ of release in 15 min. In

multi-unit dissolution (15 tablets), Imodium[®] exhibited >90% release but SJU tablets showed <5% of release thus demonstrating its ability to deter multi-dose oral abuse.

DEDICATION

With utmost respect and fulfilled heart I would like to express my deepest gratitude and bow my head towards the Supreme Personality of God head “**LORD SHRI KRISHNA**” and my **parents** for giving me blessings and power to face challenges whenever I was in need.

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ABBREVIATIONS

USFDA- United states Food and Drug Administration

NSAID- Non-steroidal anti-inflammatory drug

IN- Intranasal

IV- Intravenous

ER- Extended release

IR- Immediate release

CDER- Center for drug evaluation and research

ADF- Abuse deterrent formulation

NPS- Novel Psycho active substances

OTC- Over the counter

MET-Metformin Hydrochloride

LPH- Loperamide Hydrochloride

HME- Hot melt extrusion

FDM- Fused deposition modeling

DOE- Design of experiment

QBD- Quality by design

HPMC- Hydroxy propyl methyl cellulose

PLA- Polylactic acid

PVP- Polyvinyl pyrrolidone

PVA- Poly Vinyl alcohol

HPC- Hydroxypropyl cellulose

DSC-Differential scanning calorimetry

XRPD- X-ray powder diffraction

BE- Bigger egglet

SE- Smaller egglet

RPM- Rotations per minute

QTPP-Quality target product profile

CQA-Critical quality attributes

D85- Time for 85% of cumulative drug release

%S_{ext} - Percentage of drug extracted using water in 5 min

API- Active Pharmaceutical Ingredient

CNS- Central nervous system

BBB- Blood brain Barrier

USP- United states Pharmacopoeia

NPDS- National Poison data Base

HPLC-High Pressure Liquid Chromatography

FaSSGF- Fasted state simulated gastric fluid

FeSSGF- Fed state simulated gastric fluid

FaSSIF- Fasted state simulated intestinal fluid

FeSSIF-Fed state simulated intestinal fluid

ANOVA- Analysis of Variance

TGA- Thermo gravimetric Analysis

L/D- Length/ Diameter

ACN- Acetonitrile

1. Introduction

1.1. Opioid epidemic

Pain is an important condition that requires medical attention. Pain can be either chronic or acute. Generally non-steroidal anti-inflammatory (NSAID) and opioid drugs are used to treat or reduce pain. NSAID is responsible for blocking the function of the enzyme cyclooxygenase which leads to prostaglandins synthesis. However, opioid analgesics work as an agonist on opioid receptors located in central and peripheral nervous system. Based on the differences in their mechanisms of action, opioid analgesics are more effective than NSAID in treating most severe cases of pain (Rahman et al., 2016). Commonly used opioid drugs include morphine, codeine, oxymorphone, oxycodone and heroin, which can be administered by various routes: oral, rectal, sublingual, transdermal, subcutaneous, intramuscular, intravenous, or neuraxial (Maincent and Zhang, 2016; Rahman et al., 2017). In the past few years, prescription drug abuse has gained a lot of attention and is a rapidly growing concern in United States (Rahman et al., 2016; Schaeffer, 2012). Abusers use various paraphernalia for physical manipulation of opioid drugs as shown in Fig. 1. (Park and Otte, 2019). Prescription opioids are preferred amongst abusers. The United States Food and Drug Administration (USFDA) defines abuse as an intentional and

nontherapeutic use of drug product or any substance to achieve a physiological or psychological effect (Administration, 2017; Food and Administration, 2015). Misuse refers to inappropriate intentional therapeutic use of a drug substance specifically excluding abuse (Administration, 2017; Food and Administration, 2015; Katz et al., 2007). In 2016, 433,000 deaths were recorded due to lawful and unlawful use of opioids. The overall medical and productivity loss costs occurred with prescription opioid analgesic misuse, abuse, and deviation are accounted to be \$78.5 billion annually (Cohen et al., 2018). Opioid drugs and their derivative products are potential candidates for misuse and abuse due to euphoric effects from their use. These drugs, being easily available to the target population, have been largely misused or abused via physical or chemical manipulation to attain elevated drug concentrations in the body (Maddineni et al., 2014).

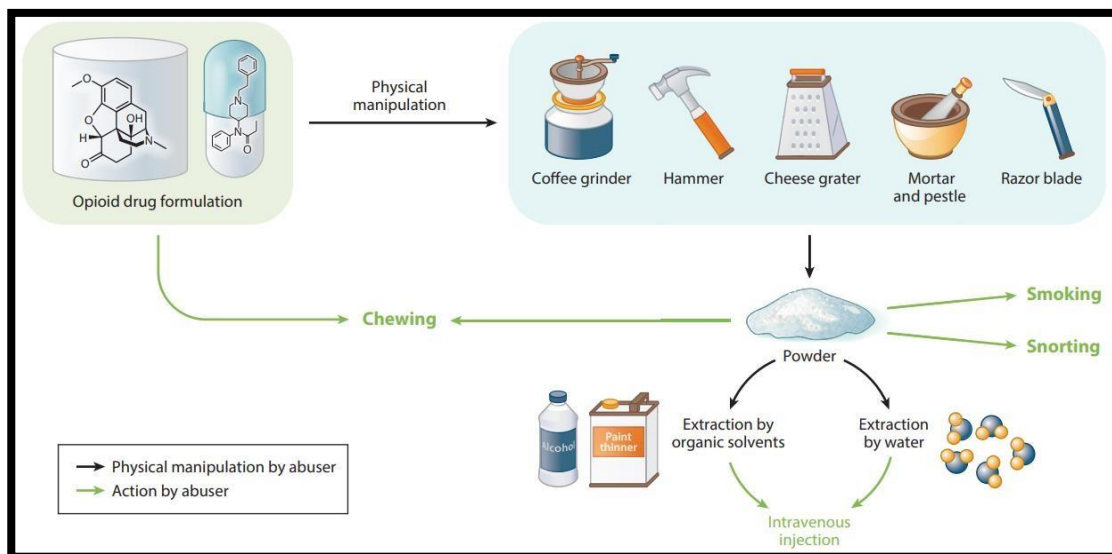


Fig. 1. Various Paraphernalia used for Physical manipulation.
(Adapted from Park and Otte, 2019)

1.2. Various routes of abuse

Most approved opioid drugs currently on the market are formulated for oral route of administration (e.g., Tablets, capsules, solutions, etc.) (Xu et al., 2016). The undesired effects of opioid misuse may vary depending on the preferred route of administration (Maddineni et al., 2014). Opioid drugs can be abused through ingestion (chewing or oral/ intake exceeding the recommended dose), inhalation (snorting, smoking or inhaling) and injection (intravenous, intramuscular, or subcutaneous administration) to attain “high effect” (Meruva and Donovan, 2019, 2020; Pergolizzi Jr et al., 2018). Often, an abuser will crush or grind the prescription opioid into a ground powder or fine particles followed by nasal insufflation, or by dissolving it in solvents such as ethanol and water for injection as shown in Fig. 2. (Rahman et al., 2017). Nonmedical use of prescription opioids through nonoral route has been associated with several adverse effects from intranasal (IN) abuse and can lead to the destruction of the nasal and palatal tissue. Abuse through intravenous (IV) routes can cause viral infections due to needle sharing and reuse of same needle. There has been a rise in abuse of extended release (ER) dosage forms due to fact that there is a higher amount of drug per unit dosage form. While immediate formulations (IR) of the same opioid has smaller dose of drug per unit dosage form (Maddineni et al., 2014; Xu et al.,

2016). Differences in pharmacokinetic profile are reported from tablet crushing, and these variations range from moderate changes to complete profile change (Maincent and Zhang, 2016; Schaeffer, 2012). Overall, the oral route is the preferred choice, followed by snorting and injection. Yet, the highest mortality and severe morbidity rates are caused by parenteral and nasal routes (Xu et al., 2016).

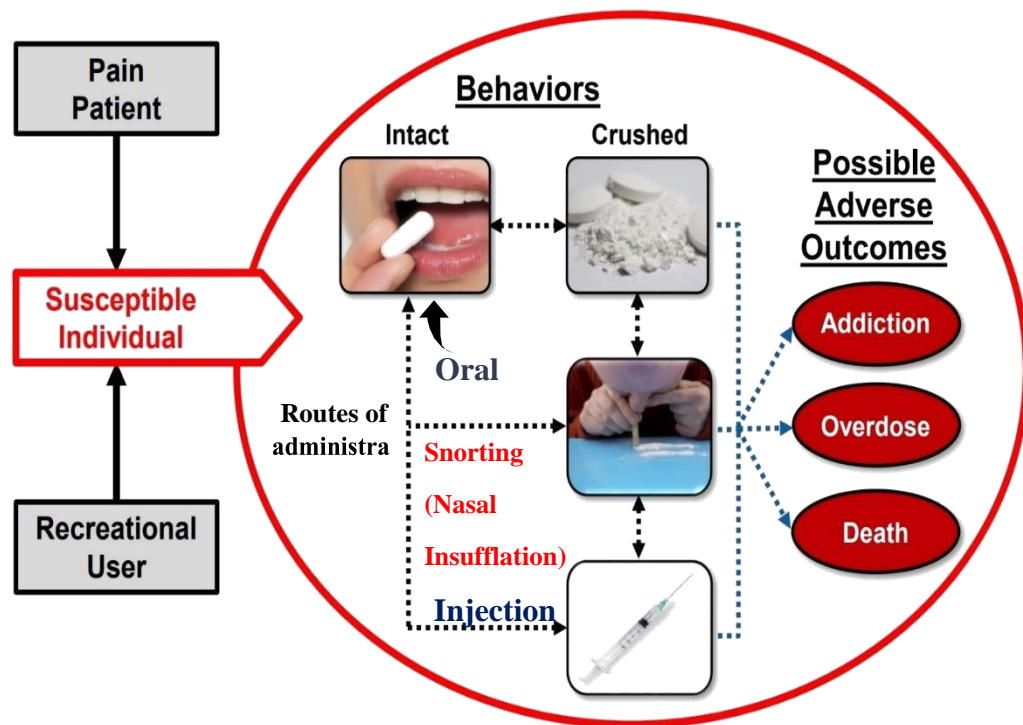


Fig. 2. Various routes of Abuse.
(Adapted from Rahman et al., 2017)

1.3. Emergence of Abuse deterrent formulations

To fight prescription opioid abuse, pharmaceutical manufacturers and the USFDA are confronting this issue by coming up with a novel concept of abuse deterrent formulations (ADFs). The USFDA and CDER (Center for drug evaluation and research) has initially issued its guidance to industry on “Abuse-Deterrent Opioids-Evaluation and Labeling in April 2015. Later in November 2017, “General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products” guidance to industry has been released by the USFDA and CDER. To deter the opioid abuse, various strategies including physical/chemical barriers, agonist/antagonist’s combinations, aversion, new routes of delivery system, new molecular entities and prodrugs have been investigated (Administration, 2017; Food and Administration, 2015). But essentially, ADFs will not provide resistance to abuse. The USFDA refers to these formulations designed to deter the abuse of prescription opioids as “abuse deterrent” rather than “tamper resistant”. Formulations with increased resistance to mechanical manipulation are demonstrated to have the potential to deter certain types of illicit use because they cannot be easily crushed in to forms that are readily snorted or injected. Currently, there are seven opioid formulations that have been labeled as abuse deterrent by the USFDA as shown in Table 1(Peacock et al., 2019). Many other

formulations and technologies with progressively improved abuse deterrence properties are currently being evaluated (Administration, 2017; Alexander et al., 2014; Boyce et al., 2018a; Cohen et al., 2018; Food and Administration, 2015; Khan and Gharibo, 2010; Marnoor, 2016; Schaeffer, 2012). The USFDA has outlined 4 categories (Table 2) to evaluate abuse deterrent properties (Food and Administration, 2015).

Table 1. Various abuse deterrent products with its marketing status
(Adapted from Peacock et al., 2019)

Product	Active Ingredient/Release	Marketing status
Oxycontin	Oxycodone HCl/ER	Prescription
Embeda	Morphine Sulfate; Naltrexone HCl/ER	Prescription
Hysingla ER	Hydrocodone Bitartrate/ER	Prescription
MorphaBond ER	Morphine Sulfate/ER	Prescription
Xtampza ER	Oxycodone/ER	Prescription
Arymo ER	Morphine Sulfate/ER	Prescription
RoxyBond	Oxycodone HCl/IR	Discontinued

Table 2. Categories for evaluation of abuse deterrent properties
(Adapted from Food and Administration, 2015)

Category 1: Laboratory-based in vitro manipulation and extraction studies	To evaluate with which abuse deterrent properties can be defeated or compromised.
Category 2: Pharmacokinetic studies	Understand the in vivo properties of the formulation by comparing pharmacokinetic profiles of manipulate and intact formulations.
Category 3: Clinical abuse potential studies	Applying clinical abuse potential studies to assess the potentially abuse deterrent properties.
Category 4: Post marketing studies	Understand the in vivo properties of the formulation by comparing PK profiles.

1.4. Impact of Abuse deterrent formulations on progressive shift to abuse of IR opioids

Economic modeling analyses indicate that ADF opioids have the potential to substantially reduce the incidence of opioid abuse in prescribed chronic pain patients relative to non-ADF opioids, but at significantly lower cost to the health care system (Severtson et al., 2016). ADFs are less attractive to abusers than available non ADF products because these formulations by definition are designed to defeat the abuser's manipulation there by making it less rewarding and more challenging (Katz et al., 2011). The rate of intentional abuse, based on US Poison Center Program data, has been reduced by approximately 75% since the past 5-year period after the approval of an ADF of oxycodone (Severtson et al., 2016; Wening et al., 2017). After the introduction of ADFs for ER opioids, there is a substantial increase in abuse of IR opioids was observed due to its availability and ease of abuse compared to ER formulations (Cicero et al., 2017; Iwanicki et al., 2016). Additionally, in between 2009 -2015 IR opioids were prescribed in higher rate of 12-16 times compared to ER opioids (Iwanicki et al., 2016). Numerous reports indicate that intentional abuse of IR opioids was about 5 folds higher on comparison with ER opioids (Cicero et al., 2017).

Chewing and snorting are the most common way to abuse an IR product (Beaumont et al., 2018; Wening et al., 2017).

1.5. Abuse of Novel psycho active substances

Due to the limited availability of prescription opioids and emergence of ADF's by the USFDA, the modern-day abusers have been shifting towards novel psycho active substances (NPS). A range of prescription (e.g. Pregabalin, Gabapentin etc.) and over the counter (OTC) drugs (e.g. Loperamide, Dextromethorphan etc.) were categorized as NPS's due to their scope of abuse from large doses, which yields intense psychoactive action and cannot be diagnosed in drug screening. A perfect example is an OTC anti-diarrheal drug, loperamide. This OTC medication is gaining popularity as a drug of abuse for attaining euphoria and for amelioration of opioid withdrawal symptoms. Due to its ease of availability and very low price, loperamide, is gaining interest among many opioid abusers. Numerous reports indicate loperamide to be alternative for opioids. Based on the USFDA report, loperamide abuse and misuse initiates, especially at doses of 60 mg (around 30 tablets).

1.6. Literature review

Literature published in the area of abuse deterrent technology is limited, majority of available literature is through patents. However, recently research on ADF's has been emerging after the issue of the USFDA's guidance to industry. In a recent study by Rahman et al., authors investigated the effect of excipients and curing process on PolyoxTM (Polyethylene oxide) based abuse deterrent formulation prepared using direct compression. In addition, they have concluded that crush resistance was mainly imparted by PolyoxTM. Addition of excipients > 50% other than PolyoxTM was found to affect the hardness, drug extraction in solvents for abuse (Rahman et al., 2017). Inclusion of high viscosity grade polymers resulted in reduced resistance to crushing and increased resistance to solvent extraction by forming gel. In study by Maddineni et al., the authors developed an abuse deterrent dosage form from Polyethylene oxide (Polyox WSR 301) based matrix using hot melt extrusion followed by pelletizing the extrudates. However, their primary objective was to utilize design of experiments to optimize the formulation in terms of percentage of drug extracted in water and alcohol (Maddineni et al., 2014). In addition, their formulation design does not include non-Polyethylene oxide matrix and rationale for selecting formulation does not involve immediate release of drug. Wening et al., developed immediate release

ADF using hot melt extrusion technology (Wening et al., 2017). However, their rationale for formulation design did not utilize DOE. But their primary objective was based on a clinical study for comparison of *vivo* pharmacokinetic profile of IR ADF with marketed IR product of same opioid. Boyce et al., studied the nasal drug release manipulated Polyethylene oxide-based drug product using an *in vitro* vertical diffusion cell after nasal insufflation (Boyce et al., 2018b). Based on the available literature till now, there is no previous report of demonstrating the development of a formulation addressing the issue of multi dose oral abuse of loperamide hydrochloride (LPH). A recent US patent by Shah N. H. and co-workers demonstrated an application of multi-particulate system with functionality coatings in limiting overdose and abuse of an opioid drugs. Investigators have developed an enteric coated crush resistant granules of oxycodone HCl and other opioids (Shah et al., 2019). Most of the ADF formulations developed using conventional methods possess many steps of processing like granulation, milling, punching, coating, curing etc. This requires higher cost and additional time for development.

1.7. Hot melt extrusion

Hot melt extrusion (HME) is a novel and viable method adopted by pharmaceutical industry for enhancing the bioavailability of poorly soluble drugs through formation of molecular dispersions (Repka et al., 2008). In HME, initially crystalline API and polymer were physically blended, later processed through different heating zones as shown in Fig. 3 (Kolter et al., 2012). Within those heating zones the API polymeric mixture gets mixed, melted and exits as a filament. This process majorly yields a solid dispersion, in majority of the cases it forms a molecular dispersion. With HME, the drug is dissolved usually in amorphous form within polymer at higher temperatures (above glass transition temperature of polymer) and high shear rate through twin screw extruder (Censi et al., 2018). HME is very efficient in cutting down the time and cost involved in development. Additionally, HME was recently found to be very viable in development of ADF's (Maddineni et al., 2014; Wening et al., 2017). In current study HME was utilized in development of ADF by means of physical and chemical approaches.

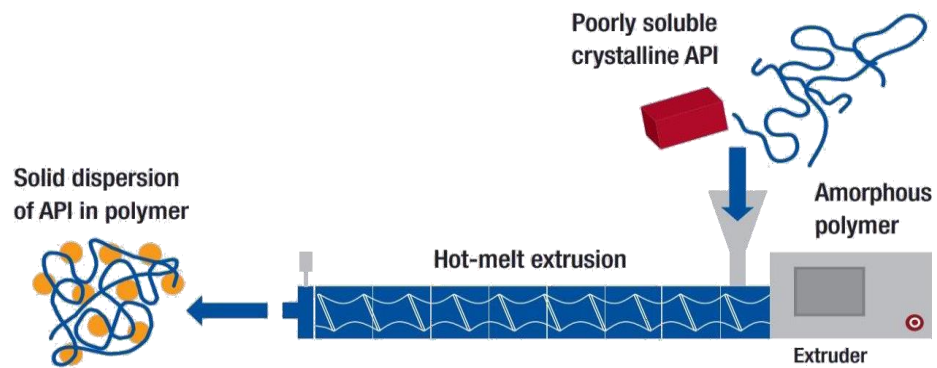


Fig. 3. Hot melt extrusion is an efficient processing method for obtaining solid dispersions. (Adapted from Kolter et al., 2012)

2. Purpose of Study

The USFDA is encouraging the development of prescription opioids with ADF's to help combat the opioid crisis. ADF's are designed to defeat the abuser's manipulation there by making it less rewarding and more challenging. HME is anovel and viable method adopted by pharmaceutical industry for enhancing the bioavailability of poorly soluble drugs through formation of molecular dispersions. HME, in conjunction with suitable polymers, has been demonstrated as a viable approach to develop dosage form with potential abuse deterrent properties. Fig. 4. Summarizes the application of HME in preparation of ADF's.

Therefore, the purpose of present research is focused on developing

- a. An immediate release ADF and evaluating based on USFDA guidance for abuse deterrence.
- b. An abuse deterrent formulation for deterring multi dose oral abuse of Loperamide Hydrochloride.

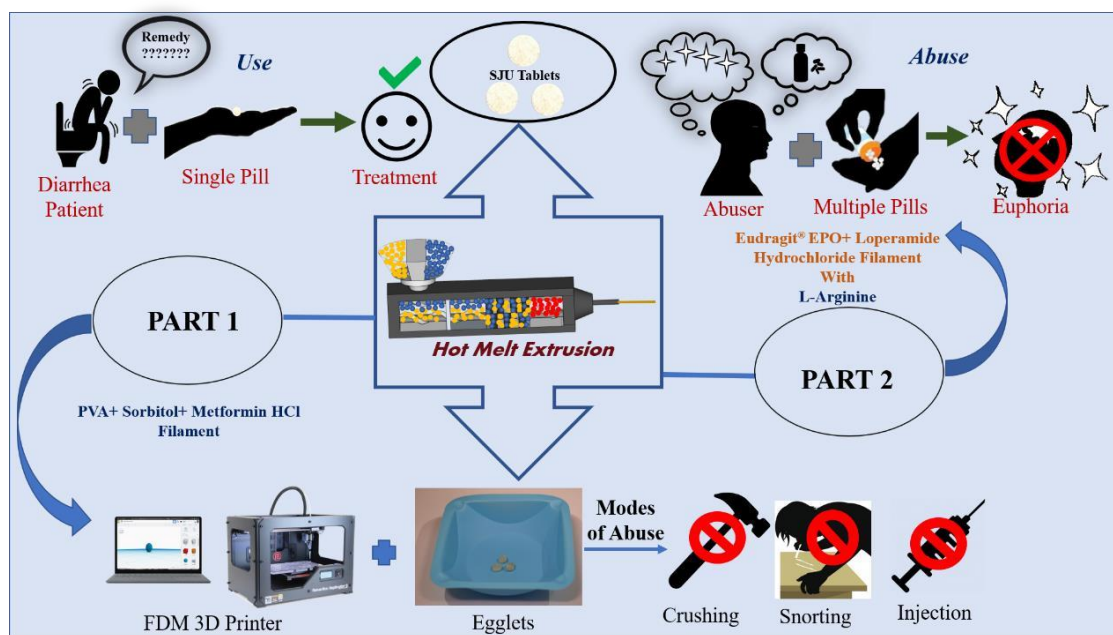


Fig. 4. Application of Hot melt extrusion in preparation of Abuse deterrent formulations.

3. Research Objectives

I) There are no previous reports or patent demonstrating application of 3D printing in the preparation of abuse deterrent formulation involving HME.

Specific Objectives include:

1. To fabricate an immediate release ADF with an ability to deter abuse through crushing, snorting, and physical manipulation.
2. Optimizing the drug release and extraction in solvents using quality by design. To achieve this aim, we explored FDM 3D printing technology to prepare an egg-shaped tablet (egglet).

The hypothesis behind selecting the egg-shaped template for printing was to resemble the hard-outer surface of an egg. The hard-outer shell deters abusers from tampering and significantly reduces the drug extraction in commonly available solvents. Further, formation of comparatively large particles up on high-pressure grounding making it resistant towards snorting.

II) There is no previous report of demonstrating the development of a formulation addressing the issue of multi dose oral abuse of Loperamide HCl through HME. This is the very first work demonstrating development of abuse deterrent loperamide hydrochloride (LPH) tablets through hot melt extrusion of gastric soluble polymer

Specific objectives include:

1. Development of ADF of Loperamide HCl using HME to deter multi dose oral abuse.
2. Identifying and optimizing the amount of free base required to raise the pH >5.
3. Development of LPH tablet formulation (SJU tablet) prepared with gastric soluble polymer with fixed amount of base.
4. Evaluation of single and multi-dose drug release of SJU tablets in bio-relevant media.

We hypothesize that tablet containing (a) small amount of base and (b) LPH incorporated into pH sensitive polymer matrix can be helpful in curbing the LPH release when multiple tablets are consumed. We anticipate that on consumption of more than 15 tablets, the amount of base will be sufficient to raise the pH above 5 at which the polymer is insoluble. This increment in the pH will hinder the release of LPH from polymeric matrix. Herewith, this technology will be referred to as “SJU technology”.

4. Abuse Deterrent Immediate Release Egg-Shaped Tablet (Egglets) Using 3D Printing Technology: Quality by Design to Optimize Drug Release and Extraction

4.1. Introduction

4.1.2. Drug (Metformin Hydrochloride)

Due to limitations in procurement of opioid drugs for conducting research model drug was used in place of opioid drug. Metformin hydrochloride (MET) was chosen as a model drug due to its similarity in aqueous and alcohol solubility with opioid drug oxycodone hydrochloride. The drug properties of Metformin Hydrochloride and Oxycodone Hydrochloride were given in Table 3 and Table 4 (Ben-Hander et al., 2015; Kasim et al., 2004; Kortejärvi et al., 2014). There are literature reports indicating the use of MET as a model drug in research on developing ADF's (Patel et al., 2018).

Table 3. Drug Information (Metformin Hydrochloride)

(Adapted from Ben- Hander et al., 2015; Kasim et al., 2004; Kortejärvi et al., 2014)

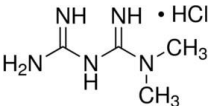
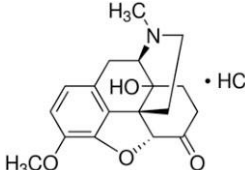
Name	Metformin Hydrochloride
Chemical Name	1,1-Dimethylbiguanide hydrochloride
Molecular formula	$C_4H_{12}ClN_5$
Molecular weight	162.52 g/mol
Structure	
CAS No.	1115-70-4
Description	Hydrochloride salt of the biguanide metformin
Melting point	223°C-226°C
Partition coefficient	0.15
Solubility	Freely soluble in water 100 g/L and slightly soluble in alcohol
BCS class	Class III

Table 4. Drug Information (Oxycodone Hydrochloride)

(Adapted from Ben- Hander et al., 2015; Kasim et al., 2004; Kortejärvi et al., 2014)

Name	Oxycodone Hydrochloride
Chemical Name	4,5-epoxy-14-hydroxy-3-methoxy-17methylmorphinan-6-onehydrochloride
Molecular formula	$C_{18}H_{21}NO_4HCl$
Molecular weight	351.83 g/mol
Structure	
CAS No.	n/a
Description	Hydrochloride salt of Oxycodone
Melting point	218°C-223°C
Partition coefficient	0.7
Solubility	Freely soluble in water 100 mg/mL and slightly soluble in alcohol
BCS class	Class I

4.1.3. 3D Printing

3D printing is an additive manufacturing technology, in which layers of material are formed under computer control to develop 3D products (Okwuosa et al., 2016). Attention has shifted towards 3D printing after the USFDA approval of ‘Spritam®’, the first 3D-printed fast-dissolving tablet in late 2015, which utilizes powder adhering ZipDose™ technique in printing porous tablets (Nukala et al., 2019c; Skowyra et al., 2015). Recently, 3D printing technology has set the platform for patient-tailored dosage form where fabrication of dosage form can be carried out in desired dose, shape and size, which is difficult to achieve using traditional technologies (Fig. 5.) (Jamróz et al., 2018). Various 3D printing technologies used for printing pharmaceuticals are binder jet printing, fused deposition modeling (FDM), semisolid extrusion, selective laser sintering and stereolithography (Yang et al., 2018). The properties of 3D-printed formulations vary with the technology opted for printing (Nukala et al., 2019c).

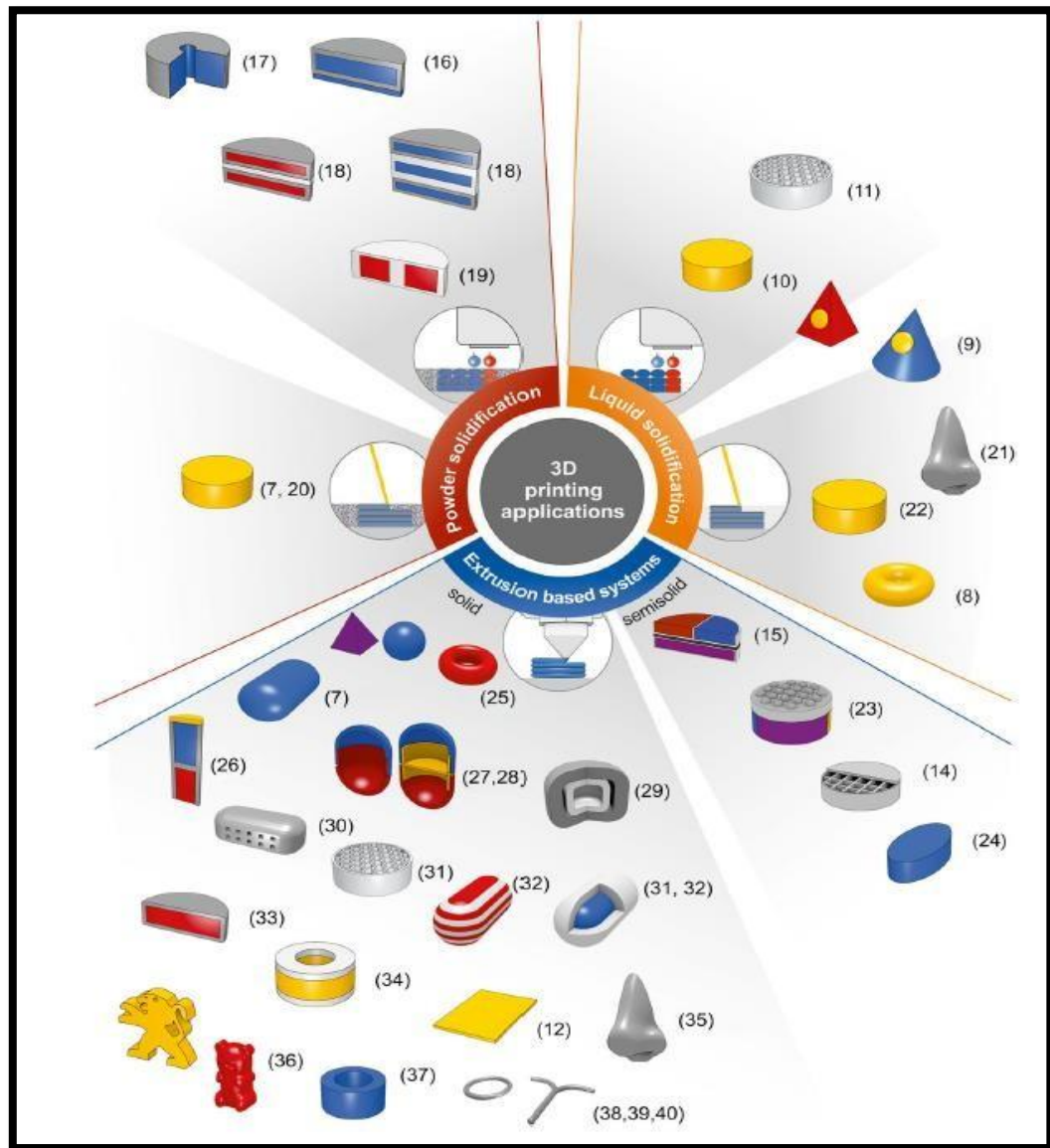


Fig. 5. Application of 3D Printing technology in printing in Various Shapes, sizes, models, Channeled printlets, various densities (infill).

(Adapted from Jamróz et al., 2018)

4.1.4. FDM 3D Printing

FDM 3D printing is one of the emerging technologies in the field of pharmaceuticals (Nukala et al., 2019c). In this technique, drug-loaded polymeric filaments (prepared using hot melt extrusion) are converted into solid dosage form of desired size and shape using a desktop 3D printer. Recently, the research utilizing FDM 3D printing technology in fabrication of oral dosage forms is on the rise (Palekar et al., 2019). FDM 3D printing would help in the fabrication of customized tablets with precision and ease compared with powder compaction, which is always done in bulk. In FDM 3D printing, initially digital 3D design is prepared using computer-aided design software. Later the design is imported to FDM 3D printer, next the filament is passed through the heated nozzle and extruded material is deposited on the build plate to prepare the desired object. The drug-loaded filaments are prepared using HME and used for FDM 3D printing as shown in (Fig. 6 and Fig. 7) (Zhang et al., 2017). Fabrication of dosage form can be done in various doses, shapes and sizes using the same equipment and drug loaded filaments (Skowrya et al., 2015). The drug release and rate can be modified by varying the size and shape of the dosage form, which can improve patient compliance (Okwuosa et al., 2016).

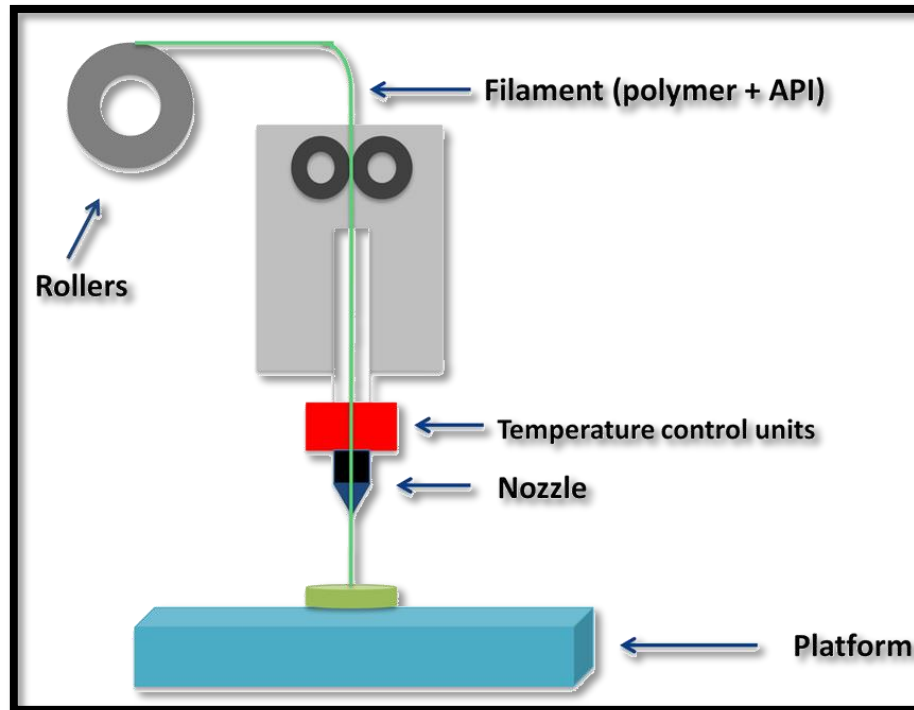


Fig. 6. Schematic Picture of desktop FDM 3D printer.
(Adapted from Zhang et al., 2017)

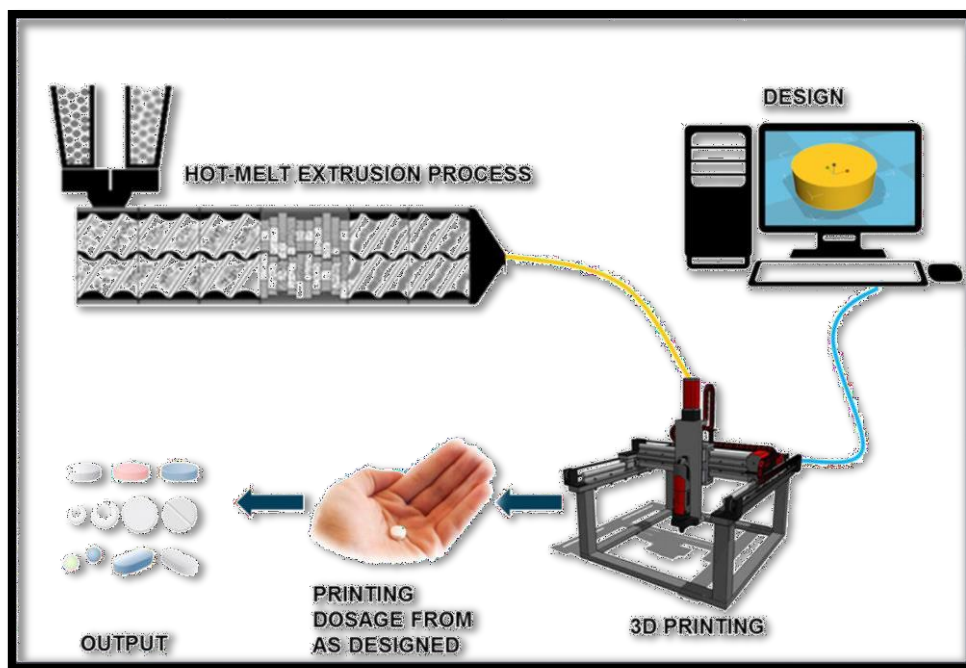


Fig. 7. Coupling 3D printing with hot-melt extrusion to produce tablets.
(Adapted from Zhang et al., 2017)

4.1.5. Limitations of FDM 3D Printing

The major limitations of existing FDM3D printing of pharmaceutical dosage form are high printing temperatures and printability of pharmaceutical polymers. In addition, polymer must be biocompatible, thermoplastic and heat stable for manufacturing using FDM 3D printing (Goyanes et al., 2015). The filaments should have tensile strength to be pushed by drive gear into the heated nozzle; the polymeric filaments of many pharmaceutical polymer do not exhibit tensile strength for 3D printing (Zhang et al., 2017). Moreover, polymer should have low glass transition temperature to conduct printing at lower temperature (Goole and Amighi, 2016). Pharmaceutical grade polymers explored for 3D printing are Eudragit® RL, Eudragit®RS, Eudragit®E, Eudragit®EPO, hydroxypropyl methylcellulose (HPMC), polylactic acid (PLA), polyvinyl pyrrolidone (PVP) and polyvinyl alcohol (PVA) (Nukala et al., 2019c).

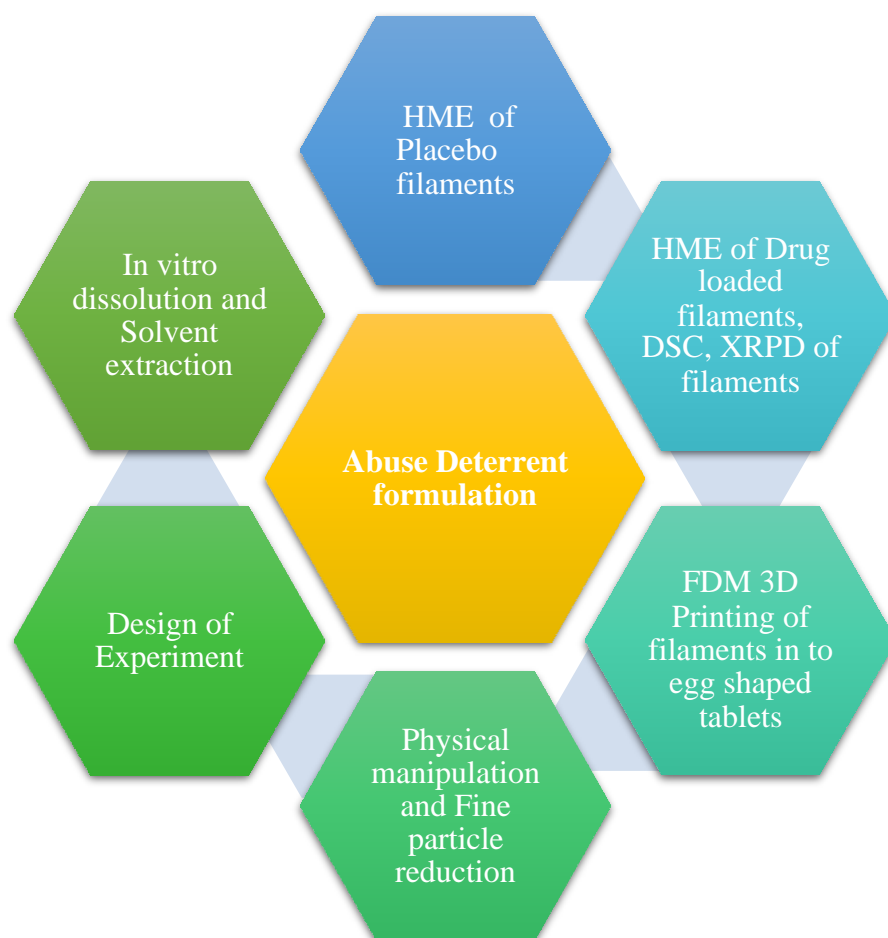


Fig. 8. Schematic diagram of proposed study (MET).

4.2. Materials

MET (>99%) was purchased from TCI America (Cambridge, MA). Parateck[®] MXP (polyvinyl alcohol) and Parateck[®] SI 150 (sorbitol) were generously gifted by EMD MilliporeSigma (Burlington, MA), and Klucel[™] (hydroxypropyl cellulose) was obtained from Ashland (Covington, KY). Kollidon[®] VA 64 (vinylpyrrolidone-vinyl acetate copolymer) and Affinisol[™] 15LV were received as gift samples from BASF (Iselin, NJ) and Dow Chemical Company (Midland, MI), respectively. Hydrochloric acid, ethanol, acetone, and other solvents were purchased from Fisher Scientific (Pittsburgh, MA). All materials were used as received.

4.3. Methods

4.3.1. Analytical Method (UV Spectroscopy)

Drug content analysis was carried out by UV spectrophotometer (BioTek Winooski, VT). Briefly accurately weighed drug was dissolved in distilled water to prepare a stock solution of 1 mg/mL. The solution was further diluted to prepare solutions of 10, 20, 30, 40, 50, and 100 $\mu\text{g/mL}$. The diluted solutions were analyzed at an absorbance wavelength of (λ_{max} 220 nm). The absorbance of each solution was measured in triplicate (n=3). The calibration curve of $Y = 0.0522x + 0.0722$ was acquired for metformin hydrochloride; $R^2 = 0.9999$.

4.3.2. Hot melt extrusion of placebo polymers

Various hydrophilic polymers were screened with an aim to identify a suitable polymeric matrix for preparation of an abuse deterrent/tamper-resistant formulation. Initial optimization of polymeric matrix was based on two criteria: printability and crush resistance. We have evaluated various polymeric filaments for their ease of printability and hardness required for crush resistance as per the USFDA guidance (>50 kg). Placebo polymeric (no drug loaded) filaments (1.5 mm diameter) of polyvinyl alcohol (PVA), hydroxypropyl cellulose (HPC) and Kollidon® VA64, Affinisol™ 15LV, and Kollicoat® IR with/without plasticizer were prepared by hot melt extrusion using twin screw extruder. In this study, instead of conventional-grade PVA, Parteck®MXP—a newly developed HME grade of PVA—was used (Palekar et al., 2019). A parallel 11-mm twin screw extruder (Process 11 Thermo Fisher Scientific, Waltham, MA) with eight electric heating zones with an L/D ratio of 40 was used for extrusion. Accurately weighed individual polymer and sorbitol were mixed in weight ratio of 9:1 using a mortar and pestle followed by thorough blending in a Turbula® mixer (Glen Mills, Clifton, NJ) for 5 min to obtain homogenous blends. The screw design of extruder was designed to have three kneading zones along with conveying zones to impart proper mixing during extrusion. PVA blends were processed at 170°C

while other polymeric blends were extruded at 140–150°C. Blends were processed at a feed rate of 2 g/min through hopper to heated barrel followed by extrusion at a screw speed of 100 RPM. Output through 1.5 mm circular die converted molten mixture into suitable filaments which can be used as a feed stock to 3D printer. The temperature of die was maintained at 150°C during extrusion. Additionally, a conveyer belt was equipped next to die to cool and straighten the filaments exiting die. Filaments of desired length were cut from the conveyer belt and stored at room temperature in sealed bags prior to printing.

4.3.3. Hot melt extrusion of drug loaded filaments

From the polymer screening, PVA and sorbitol mixture filaments possessed required criteria for 3D printing and crush resistance as per the USFDA guidance compared to other polymeric filaments and hence, PVA and sorbitol mixture was selected for further studies. In preparation of drug loaded filaments, accurately weighed MET, PVA and sorbitol were physically mixed in a mortar and pestle followed by thorough blending in a Turbula[®] mixer (Glen Mills, Clifton, NJ) for 5 minutes to obtain homogenous blends. Physical mixtures were prepared in a weight ratio of 8.5:1:0.5, 8:1:1, 7.5:1:1.5 PVA: sorbitol: MET respectively, to obtain extrudates with 5% w/w, 10% w/w, 15% w/w drug loading (Table 5). Extrusion was carried out at 170° C with a screw speed of 100 RPM. Torque was analyzed during the extrusion. The obtained filaments were stored in sealed clear bags at room temperature.

Table 5. Composition of drug loaded mixtures processed through HME

PVA (w/w %)	Sorbitol (w/w %)	Drug (w/w %)
85	10	5
80	10	10
75	10	15

PVA Polyvinyl alcohol

4.3.4. Solid state characterization

Characterization of the different components was carried out by differential scanning calorimetry (DSC) and x-ray powder diffraction (XRPD).

4.3.4.1. Differential scanning calorimetry

Differential scanning calorimetry (DSC) thermograms of pure excipients, drug, and crushed filament were obtained using a Q200 modulated DSC instrument (TA instruments, New Castle, Delaware). Accurately, weighed samples (5 mg) were hermetically sealed in an aluminum pan. The samples were equilibrated at 25°C and then heated from 25 to 250°C at a ramp of 2.5°C/min. Analysis was performed using a Q2000 analysis software provided by TA.

4.3.4.2. X-ray powder diffraction

X-ray powder diffraction (XRPD) of pure excipients, drug, and crushed filament was performed using a Shimadzu 6000 X-ray diffractometer (Shimadzu Corporation, Kyoto, Japan) with Cu-K α monochromator emitting x-rays. Radiations of 60 kV and 55 mA was used for analysis between 10 and 60° at a ramp of 2°/min. Samples were placed in glass cavities and were compressed using a glass slide for even distribution of the surface.

4.3.5. Egglet shaped 3D printing of MET extrudates

MakerBot® Replicator 2 desktop single nozzle 3D printer (MakerBot Inc., USA) with 0.4-mm nozzle was used for fabricating egglets. Initial template for oval tablets, i.e., egg-shaped tablets (egglets) were designed using TinkerCad online 3D designing software and saved in .stl file format. Design was imported to 3D printer software MakerWare™ (v. 2.2.2). The oval design was selected based on structural integrity and its geometry for crush resistance.

It was hypothesized that, when force applied to an egglet versus a conventional tablet (flat and round), the distribution may not be uniform in oval shape, due to the bulge in the Z-axis across. Egglets were printed using MET-loaded filaments as feed to printer. Dimensions of small egglet (SE) and big egglet (BE) are given in Table 6. Printing was done in two infill percentages (density) 45% and 90% in hexagonal printing infill pattern.

The following printer settings were utilized for printing: standard resolution without activating the raft, supporting and bridging option, nozzle temperature was set at 200°C (lower temperatures resulted irregular deposition), build plate was maintained at room temperature, printing speed of extruder was set at 45 mm/s while extruding and 150 mm/s when traveling. Printing was performed with a set top and bottom layer thickness of 1.6 mm and 1.6 mm respectively (to mimic the hard upper and lower shells of egg), by using two shells and 0.4 mm layer height. Precut Kapton tape was applied to the build platform for proper adherence of model to the surface. The individual weights of all egglets printed were mentioned in Table 7.

Table 6. Dimensions of egglets

Dimension	BE	SE
X	8 mm	6 mm
Y	5.5 mm	4.4 mm
Z	5 mm	3.3 mm

BE Bigger egglet *SE* Smaller egglet

Table 7. Individual weights of egglets printed

Run	A: Drug load (%)	B: Infill density (%)	C: X (mm)	D: Y(mm)	E: Z (mm)	Weight(mg)	Drug (mg)
1	10	45	6	4	3.3	100	10
2	5	90	8	5.5	5	250	12.5
3	10	45	8	5.5	5	200	20
4	15	90	8	5.5	5	250	37.5
5	5	45	6	4	3.3	100	5
6	10	90	8	5.5	5	250	25
7	15	90	6	4	3.3	150	22.5
8	15	45	8	5.5	5	200	30
9	5	90	6	4	3.3	150	7.5
10	10	90	6	4	3.3	150	15
11	5	45	8	5.5	5	200	10
12	15	45	6	4	3.3	100	15

4.3.6. Hardness/Crush resistance and friability testing

Pharmaceutical hardness tester (Pharma Alliance Group, CA, USA) was used for characterizing the egglets' hardness. The hardness tester was able to exert a maximum load of 50 kg (~ 500 N). All the measurements were done in triplicate. Friability test was performed using a HT-2 Friabilator USP (Sotax, Switzerland). Egglets (n = 10) were preweighed and placed inside the friabilator and rotated at a speed 25 RPM for 4 min. The egglets were reweighed and the percentage weight loss was calculated.

4.3.7. Physical manipulation and fine particle reduction

Physical manipulation was carried out by using mechanical and power-driven electrical means. Common household equipment such as a knife, hammer, spoons, and graters were used to check the physical mechanical manipulation. Additionally, household electrical appliances with high shear, i.e., a coffee grinder (Brewberry, Bangkok) and laboratory equipment's like a mortar and pestle, high shear analytical mill were also employed. The egglets were subjected to different manipulation conditions with varied levels of stress conditions for each equipment. Egglets were subjected to high shear grinding for 5 min using a coffee grinder and analytical mill. The resultant material was subjected to particle size distribution by sieve analysis.

4.3.8. *In vitro* drug dissolution

In vitro drug release was performed using USP II dissolution apparatus (Symphony 7100, Distek, New Brunswick, NJ) in 900 mL of 0.1 N hydrochloric acid (HCl). The dissolution medium was maintained at $37 \pm 0.3^{\circ}\text{C}$ and were stirred at 100 RPM paddle speed. Samples (3 mL) were withdrawn at specified time intervals of 5, 10, 15, 30, 45, and 60 min and equal volume of fresh medium was then replaced into the dissolution vessels at each time point. Drug content in collected samples was analyzed using a UV spectrophotometer at 220 nm. All dissolutions studies were carried out in triplicates ($n = 3$).

4.3.9. Solvent Extraction

USFDA recommends different levels of solvent to evaluate the drug extraction from ADF to minimize injection abuse. Drug extraction from egglets was tested using the solvents mentioned in Table 8. Initial extraction studies were carried out using level 1 solvent, i.e., deionized water. Further, level 2 and level 3 solvents were employed for extraction studies. Each egglet was added to a glass vial with 5 mL of solvent and vortexed for 30 s. After 5 min, 20 μ L of aliquots was withdrawn and diluted to 5 mL with distilled water. MET content in aliquot was analyzed using UV spectrophotometer at 220 nm. All the measurements were done in triplicates ($n = 3$).

Table 8. Various levels of solvents used for solvent extraction

Level 1	Level 2	Level 3
Deionized water	40% v/v ethanol	100% ethanol, acetone

4.3.10. Quality by Design

Response surface design was used to optimize D85 (i.e., time for 85% of cumulative drug release) and % S_{ext} (i.e., percentage of drug extracted using water in 5 min). Five definite factors which were utilized in development of formulation, i.e., drug loading (5%, 10%, and 15% w/w), infill density (45% and 90%), and dimensions (X, Y, and Z) were identified as critical quality attributes (CQA) (independent variables).

D85 and % S_{ext} were selected as responses (dependent variables). Response surface design was used to get maximum information with minimum experiments. D85 < 30 min and % S_{ext} < 20% were set as quality target product profile (QTPP).

Design Expert[®] (11.0.3.0) was used to design the experiments. Twelve experiments with different levels of factors were performed. Identification and quantification of correlation between CQAs and dependent variables were carried out and polynomial equation explaining the main effect and interaction effect were derived. The relationship between independent variables (CQAs) on responses (D85 and % Sext) was demonstrated by response surface plot with regions of maxima and minima indicated by red and blue, respectively. Design layout with factors and responses is given in Table 9. All the experiments were executed in randomized manner to minimize the bias. Analysis of variance (ANOVA) was performed to evaluate the effect of each independent variable on time needed for D85 and % S_{ext} at significance level, $\alpha = 0.05$.

Table 9. Design Layout with factors and responses

Run	Factor 1 A: Drug load (%)	Factor 2 B: Infill density (%)	Factor 3 C: X (mm)	Factor 4 D: Y (mm)	Factor 5 E: Z (mm)	D85 (min)	%S _{ext} in 5 min
1	10	45	6	4	3.3	40±2	15±5.3
2	5	90	8	5.5	5	66±1	6±3.75
3	10	45	8	5.5	5	67±3	4±2.83
4	15	90	8	5.5	5	58±2	7±2.47
5	5	45	6	4	3.3	41±1	11±2
6	10	90	8	5.5	5	64±3	6±3.5
7	15	90	6	4	3.3	40±1	12±4.4 1
8	15	45	8	5.5	5	52±4	6±0.24
9	5	90	6	4	3.3	39±2	9±3.5
10	10	90	6	4	3.3	42±1	12±5
11	5	45	8	5.5	5	60±2	4±3
12	15	45	6	4	3.3	30±1	14±1

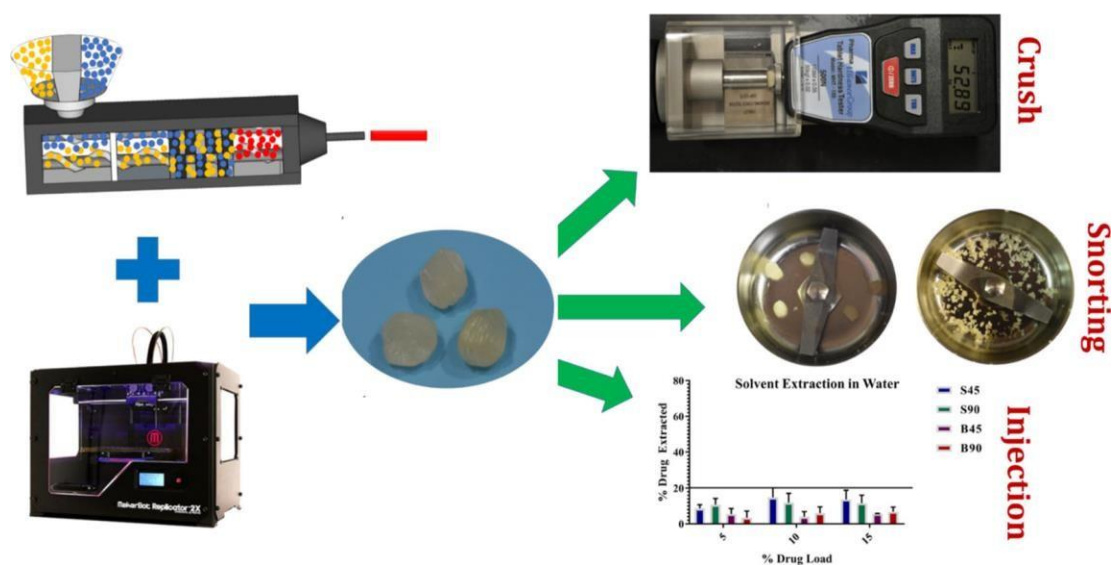
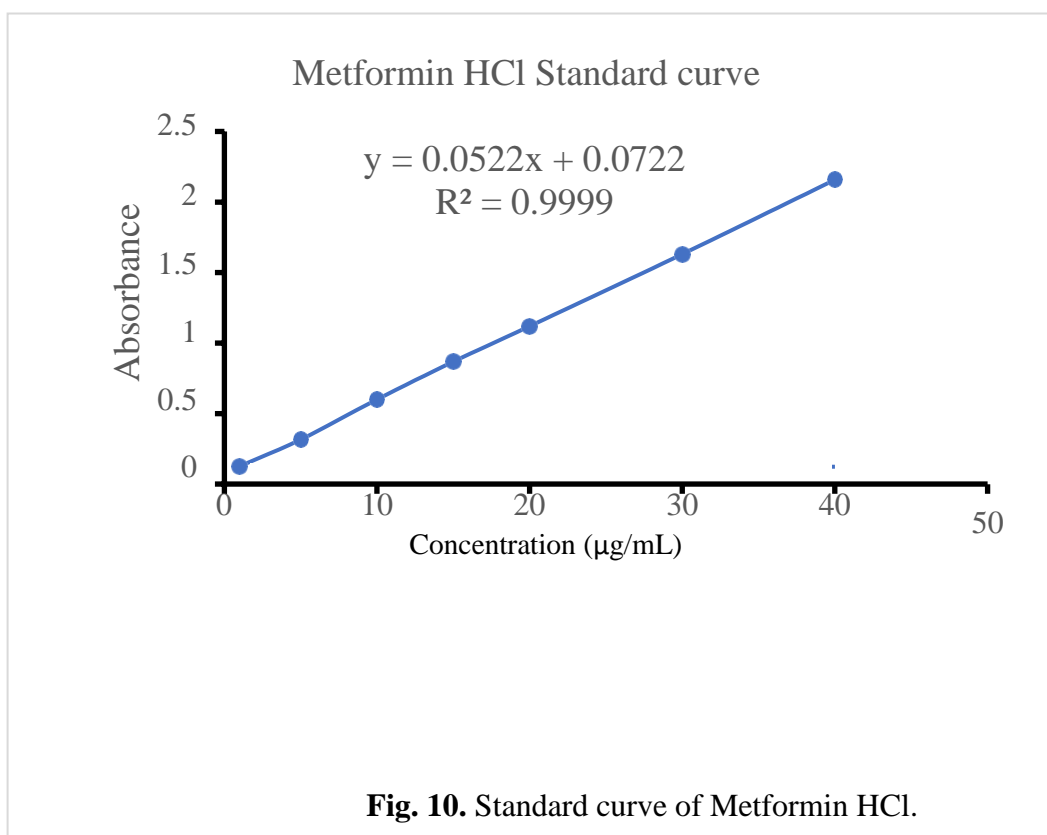


Fig. 9. Schematic representation for development and characterization of the abuse deterrent egglet.

4.4. Results and Discussion

4.4.1. Analytical Method (U.V)



4.4.2. Hot melt extrusion of placebo polymers

Printability of drug-loaded polymeric filaments through an FDM 3D printer is one of the major concerns. Not every polymer is suitable for printing. For conventional hot melt extrusion application, brittle filaments are desired because they need to be easily milled/crushed and compressed into a tablet. However, in the case of 3D printing, the filament should have necessary mechanical strength and flexibility for passing through the nozzle, i.e., the filament should possess optimum elasticity to avoid issues such as breaking and clogging the nozzle while 3D printing. Brittleness of filaments renders it difficult to print as they tend to break, and soft filaments pose a problem of getting squeezed by feeding gear inside extruder of printer. Therefore, our initial goal was to prepare HME filaments with appropriate mechanical strength to withstand force applied by the 3D printer.

Ease of printability through the FDM 3D printer and hardness of printed egglets (desired hardness > 500 N) were considered for selecting an ideal polymer for the preparation of MET-loaded ADF. Affinisol™15LV was easy to extrude through HME but its filaments were fragile enough to break on the conveyer belt itself. Filaments of Kollidon®VA64 were a little sticky. On cooling, these filaments were found to be fragile, resulting in constant breaking inside printer extruder. Filaments prepared using

combination of Kollidon[®]VA64 and Affinisol[™]15LV (1:1) possessed higher mechanical strength but too brittle for a reproducible printing. HPC filaments were too soft which resulted in squeezing of filament between feeding gears. As a result, feeding gears were unable to push the filament at constant printing speed. Filaments prepared using Kollicoat[®] IR and PVA possessed enough mechanical strength and flexibility for printing. However, egglets printed using Kollicoat[®] IR/sorbitol (90:10 w/w) filament had very low hardness < 130 N whereas, egglets prepared using PVA/ sorbitol (90:10 w/w) showed hardness of > 500 N irrespective of dimension, infill pattern, and percentage. Hence, based on printability and hardness results, PVA with 10% w/w sorbitol was found to be the most suitable polymer matrix for the preparation of immediate release egglets. The difference in the mechanical property of various polymeric filaments is due to their chemical composition. Affinisol[™]15LV and HPC are essentially a carbohydrate while PVA has a thermoplastic characteristic due to vinyl backbone.

4.4.3. Hot Melt Extrusion of Drug loaded filaments

As mentioned above, PVA with 10% w/w sorbitol was chosen as optimized polymer blend for further studies. MET loaded PVA-sorbitol filaments with 5, 10, and 15% w/w MET loading were successfully extruded with hot melt extrusion. Initially, extrusion was carried out at a barrel temperature of 140°C which resulted in hazy filaments due to incomplete melting of polymer blend. Also, at this temperature, significantly higher torque (> 70%) caused the extruder to stop automatically. At 160°C, polymer blend began to melt but MET was not thoroughly mixed with PVA. Further increase in processing temperature to 170°C resulted in formation of homogenous glassy filaments. At this temperature, the material was melting properly thus resulting in extremely low processing torque (< 15%) which was in an acceptable range of operation. It can be hypothesized that, at this processing temperature sorbitol, a thermal lubricant has maximum plasticizing capacity. Our observation was in agreement with Lang et al., 2014 (Lang et al., 2014). Plasticizing effect of sorbitol during HME of PVA was reported previously by Tian et al., 2017 and Shemis et al., 2013, where both the authors have indicated that -OH groups of sorbitol undergoes strong hydrogen bonding with PVA thereby reducing the interaction between PVA

molecules itself (Shmeis et al., 2013; Tian et al., 2017). The use sorbitol as a plasticizer was well reported in literature (Censi et al., 2018; Repka et al., 2008).

4.4.4. Solid state characterization

4.4.4.1. Differential scanning calorimetry

DSC thermograms of pure components, physical mixture, and crushed filaments are shown in Fig. 11a. DSC scan of pure MET revealed a characteristic melting endothermic peak at 225°C which was in agreement previous literature reported by Hajare et al., 2012 (Hajare and Patil, 2012). DSC scan of the physical mixture showed a similar sharp melting endothermic peak at 225°C, indicating that the crystalline nature of active pharmaceutical ingredient (API) remained unchanged by the polymer during trituration process while preparing the physical mixture. DSC scan of PVA showed characteristic T_g and T_m at 54°C and 180°C, which were in accordance with the studies reported by W. De Jaeghere et al., 2015 and manufacturer's technical information (Corporation, 2016a; De Jaeghere et al., 2015). DSC scan of sorbitol reported melting endotherm at T_m at 100°C which was in agreement with manufacturer's technical information (Corporation, 2016b). Most importantly, an absence of sharp melting endotherm of MET in DSC scan of crushed filaments suggesting amorphization of API during HME.

4.4.4.2. X-ray powder diffraction

XRPD pattern of pure components, physical mixture, and crushed filaments are shown in Fig. 11b. XRPD pattern of MET indicated distinct crystalline peaks at $2\theta = 17.5^\circ$, 24.4° , 31.3° , and 39.3° while PVA showed a broad peak between $2\theta = 19^\circ$ – 25° due to its semi-crystalline nature(De Jaeghere et al., 2015). XRPD of the physical mixture also showed sharp crystalline peaks at $2\theta = 17.6^\circ$, 24.5° , 31.3° , 39.4° denoting that the solid state of API and PVA was unaltered during trituration and blending. Characteristic crystalline peaks of API were completely absent in XRPD pattern of crushed extrudates (filaments). Crushed filaments did not show any sharp crystalline peak of MET, indicating amorphization of drug within polymer. Data of XRPD were very well in agreement with DSC results.

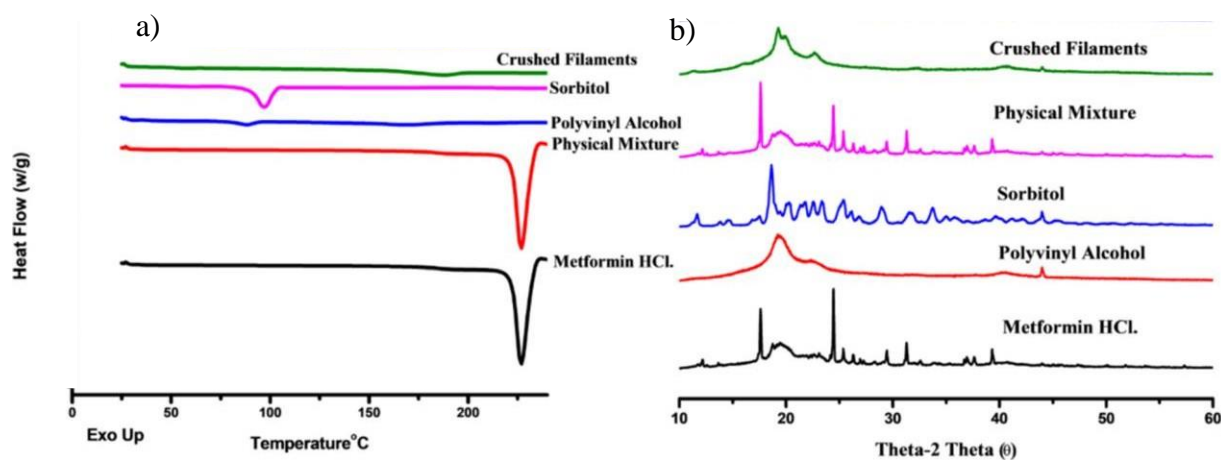


Fig. 11. Solid-state characterization

a) Differential scanning calorimetry b) X-ray powder diffraction. Absence of MET endothermic peak in DSC and absence of crystalline peak in XRPD confirmed amorphization of drug during HME.

4.4.5. Egglet-Shaped 3D Printing of MET Extrudates

The tablets were specifically printed in an egg shape with an aim to resist physical manipulations. Initially, FDM 3D printing of the extrudates to fabricate egglets was performed at different temperatures using a benchtop single nozzle FDM 3D printer (MakerBot® Replicator 2, MakerBot, Brooklyn, NY). Egglets printed using the FDM 3D printer are shown in Fig. 12. The printing was done at various temperatures to optimize the minimum temperature required for printing. Printing performed at temperatures $< 190^{\circ}\text{C}$ resulted in the improper melting of feed material from nozzle. Hence, it resulted in significant surface imperfections due to nonuniform flow of the material from the nozzle. Melting and flow of the material were found to be uniform at 200°C . Thus, 200°C was optimized as the temperature for printing. Printing performed at this temperature yielded reproducible egglets, i.e., they had a minimum weigh variation ($< 2\text{ mg}$). Fabrication was done in bigger (BE) and smaller dimensions (SE) in three drug loadings as shown in Table 6 using two infill percentages (45% and 90%) in hexagonal infill pattern. Egglets printed in SE and BE dimensions had an average printing time of 1.5 min and 2 min, respectively. Irrespective of chosen infill density, the printing time remained constant based on dimension selected.

4.4.6. Hardness/Crush resistance and friability testing

All the egglets fabricated using filaments of different drug loadings (5, 10, and 15% w/v), infill percentages (45% and 90%), and sizes were found to withstand the maximum force applied by hardness tester. Interestingly, there was no deformation or change in the shape of the egglet even at the maximum force of hardness tester. Picture of egglets before and after hardness test is shown in Fig. 12. panels a and c, respectively. We assume that such a high mechanical strength of egglet is attributed to thermoplastic behavior of PVA with sorbitol. Additionally, internal egglet integrity was due to fused polymer bridges in layer by layer fashion, along with increased thickness on both sides resulted in very high mechanical strength. Hence, every hardness test (all the formulations from run1 to run 12) yielded in force required > 500 N (50 kg) as shown in Fig. 10b. Friability was less than 0.1% for all the egglets. Therefore, it can be concluded that the egglets were crush resistant as per the USFDA guidance and previously reported literature (Administration, 2017; Cailly-Dufestel et al., 2015; Food and Administration, 2015; Maincent and Zhang, 2016). It can be potentially helpful in defeating abusers' interest towards snorting, injection, crushing, and chewing.

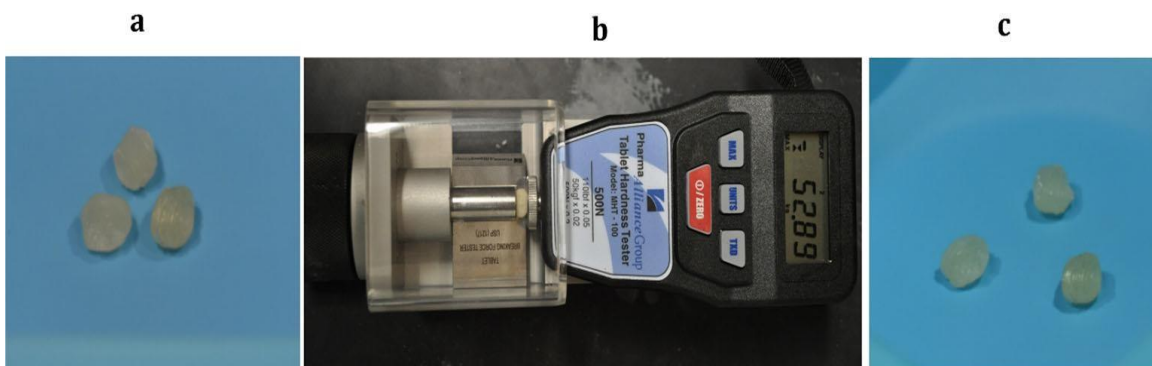


Fig. 12. USP hardness test a. Before test b. Egglet at maximum force c. After test.

4.4.7. Physical manipulation and fine particle reduction

Manipulation efforts demonstrated that egglets cannot be cut, grated, or deformed using common household equipment. Household tools have low shear mechanical forces. It was essential to evaluate it because they are readily available to tamper the formulation. Manipulations performed using high shear electric grinders and lab analytical mills yielded a coarse powder/chunky material. Fig. 13. panels a and b show egglets before and after grinding in a coffee grinder and lab analytical mill, respectively. It was important to determine the particle size distribution (PSD) of dosage form manipulated by various mechanical means to understand the scope of nasal abuse. PSD of crushed egglets revealed that majority of the particle were far bigger than the snorting range. From sieve analysis, it was observed that > 80% w/w particles were greater than 1 mm and found to be coarse/chunky material. While < 10% w/w of particles were found to be above 840 μm , and > 99% of particles were greater than snortable range (> 500 μm) of particle size form the coffee grinder (Fig. 13c). Whereas, from analytical mill >90% of particles were greater than snortable range. From an abuser's perspective, snorting is one of the preferred routes of abuse. It is one of the most convenient and major routes of abuse (Katz et al., 2011). Conventional tablet formulations are crushed to prepare a fine powder which could be inhaled

(snorted) to attain a state of euphoria (Khan and Gharibo, 2010). Intranasal inhalation can result in both bypassing the blood-brain barrier and hepatic first-pass metabolism (Maddineni et al., 2014). Whereas, nasal formulations possessing particle size of 10–20 μm is essential for application through nasal route but particle size $> 100 \mu\text{m}$ might cause nasal irritation (Fransén et al., 2007). Based on the USFDA guidance in 2015 and previous literature, when the mass percent of fine particles ($\leq 500 \mu\text{m}$) is $\leq 10\%$ then the product becomes unsuitable for nasal insufflation (Administration, 2017; Bartholomäus et al., 2013). Our study shows that even though the egglets could be crushed only by high shear milling for a longer time, it could not be crushed into fine particles viable for snorting. Thus, egglets can be an amenable method to deter abuse through tampering, injection, chewing, and snorting.

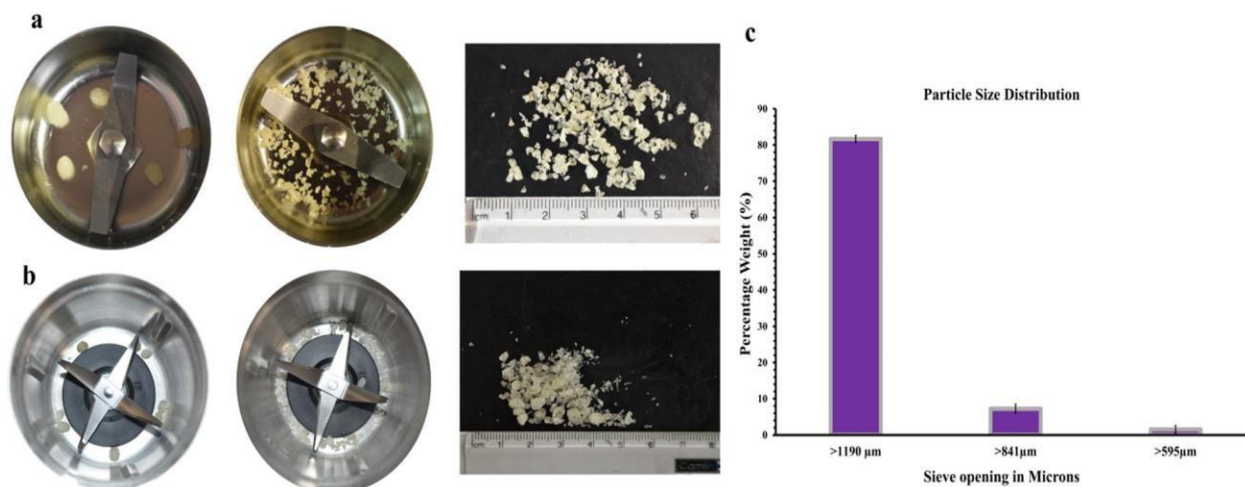


Fig. 13. Crush resistance and milling of optimized egglets in a. laboratory analytical mill and b. commercial coffee grinder and c. average particle size distribution of particles obtained after grinding in coffee grinder.

4.4.8. *In vitro* drug dissolution

The dissolution data of egglets is shown in Fig. 14. It was observed that SE with 15% w/w drug loading in smaller dimension with 45% infill density showed 85% of drug release in 30 min (Fig. 14c). On the other hand, egglets prepared using 5% w/w and 10% w/w drug loading were unable to achieve $D_{85} < 30$ min (Fig. 14 a and b). Primarily, drug loading played a vital role in dissolution rate of formulations followed by dimensions of egglets and infill density. Interestingly, egglets with 5% w/w drug loading and 90% infill density showed almost 27 min higher D_{85} for BE compared to SE. Similar trend was noted in egglets of 10% w/w and 15% w/w drug loading. Difference in D_{85} was less in egglets with 45% infill density. D_{85} was around 18 min shorter for SE compared to BE in egglets with 45% infill density. Thus, it was imperative to carry out a design of the experiment (DOE) to systemically investigate the effect of size, drug loading and infill density on D_{85} . Detailed information about factors affecting D_{85} were given in quality by design (QbD) section.

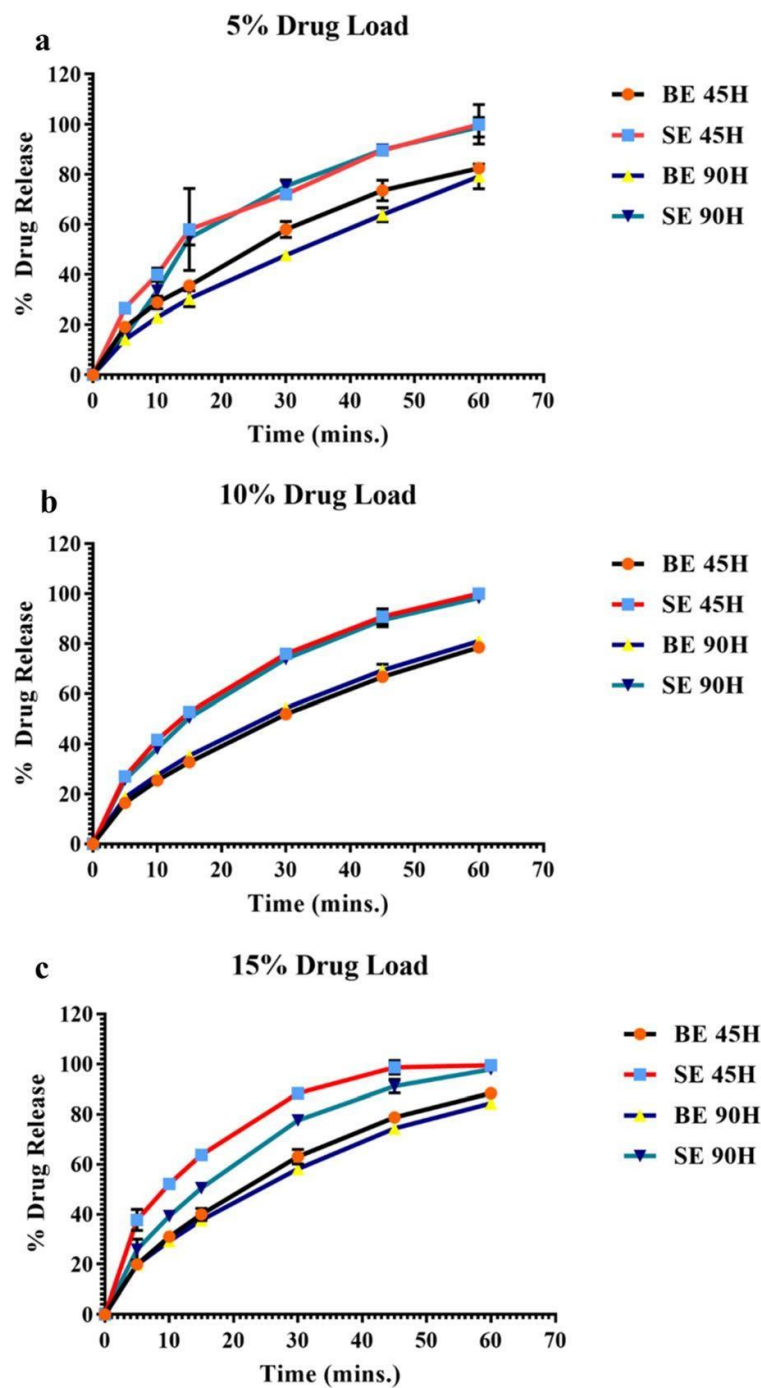


Fig. 14. *In vitro* dissolution studies of egglets in 900 mL of 0.1N HCl (n=3) a. 5% w/w drug load b. 10% w/w drug load c. 15% w/w drug load.

4.4.9. Solvent extraction

To evaluate the abuse deterrence properties for parenteral route of administration, it was essential to measure amount of drug extracted in small volume of solvent to check the viable of injection abuse. Smaller volumes of extraction solvent (5 mL) were used for the study based on the fact that more than 5 mL of volume is not suitable to fill and inject via syringe. USFDA guidance also recommends use of 5 mL extraction solvent. Another reason is to mimic the attempts to dissolve the formulation in a teaspoonful of solvent (5 mL) which was in accordance with previous literature (Cailly-Dufestel et al., 2015; Fransén et al., 2007; Kumar et al., 2013; Wening et al., 2017). Extraction studies were performed in different household solvents as per the USFDA guidance (Table 8).

Water was chosen as a first line of solvent for extraction studies as it is the most commonly available solvent for any abuser. Visual observation at 0 min (Fig. 15a) and after 5 min (Fig. 15b) in water revealed that egglets remained intact. After 5 min, egglets were vigorously vortexed for additional 10 min. But no change in egglets geometry was observed which confirmed that egglets would resist the dissolution in small volume of water. Amount of drug extracted in water depends up on infill density, dimensions, drug loading. Less than $\leq 15\%$ of drug was extracted in 5 min from all the

batches of egglets (Fig. 15c). Hence, 3D-printed egglets can also deter the abuse through parenteral route of administration.

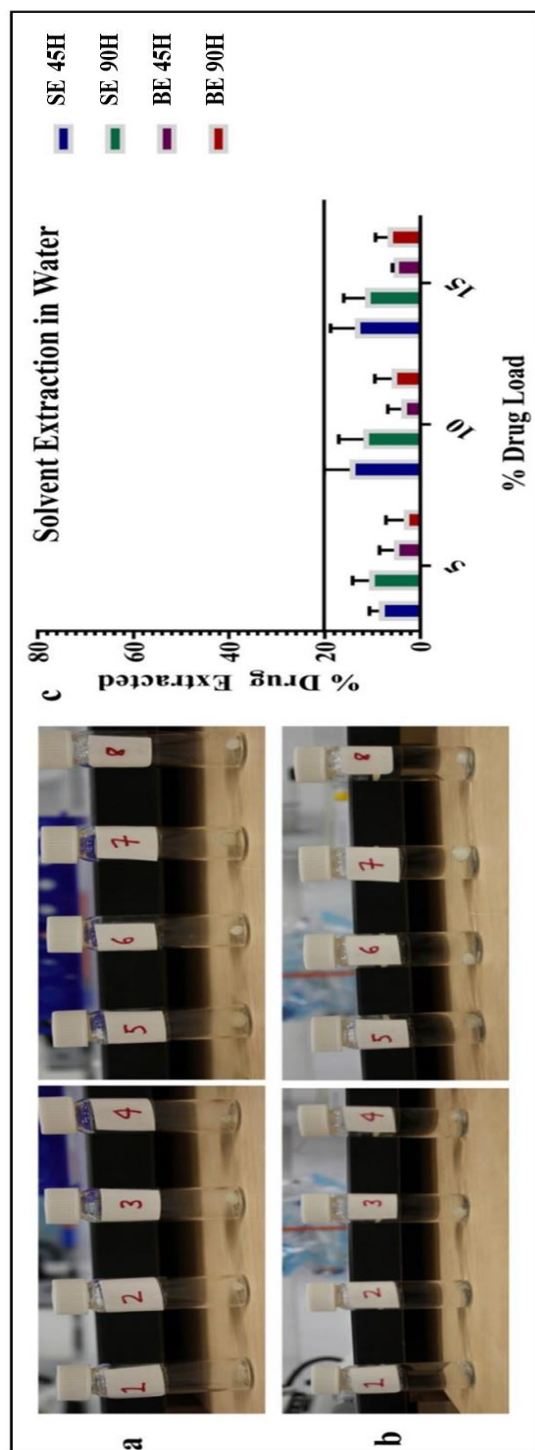


Fig. 15. Solvent extraction at different time intervals. a Time = 0 min (t_0). b Time = 5 min (t_5). c Percentage drug extraction in 5 min in 5 mL of water ($\% S_{ext}$). Solid black line indicates desired % drug extraction ($< 20\%$). All solvent extraction studies were done in triplicate ($n=3$).

4.4.10. Quality by design

Over the past decades, QbD has been promoted by the USFDA as a systematic approach to enhance pharmaceutical development through design efforts. The QbD has two main objectives: (a) designing a method in a path that pharmaceutical manufacture consistently meets critical quality attributes and (b) understanding and controlling the impact of formulation components and process parameters over critical quality attributes (Chobisa et al., 2018; Mishra and Rohera, 2017; Saurí et al., 2014). To get an insight into both the main and interaction effects of formulation and process factors, DOE have been employed. In our study, response surface design was chosen as our DOE to optimize the D85 and % S_{ext}.

4.4.10.1. Statistical analyses of responses D85

Responses obtained for D85 by changing various CQAs are shown in Table 9. ANOVA (Table 10) showed that model was significant ($p < 0.0001$). Values of coefficient of determination R^2 , adjusted R^2 , and predicted R^2 were 0.9057, 0.8847, and 0.8271, respectively. The predicted R^2 of 0.8271 was in reasonable agreement with adjusted R^2 of 0.8847. The model having difference of less than 0.2 between predicted R^2 and adjusted R^2 was good for prediction purpose. As shown in Table 10, it was evident that higher the infill degree, lesser the water penetration into the egglet, which resulted in longer D85. Increase in drug loading resulted in shorter D85. While, increase in X dimension resulted in longer D85. ANOVA (Table 10) suggested that amongst all CQAs, only X dimension was a major contributor while drug loading was not a significant factor for D85. Further based on response surface plot (Fig. 16a) and contour plot (Fig. 16b), it was clear that, infill density has no effect on D85 while it was substantially affected by drug loading, even though ANOVA states that X dimension p value is 0.0682 (Table 10).

The following polynomial equation has been generated to establish the relation

between CQAs and D85 as:

Actual Equation: $D85 = -22.68917 - 0.631250 * \text{Drug load} + 11.27333 * X$ (1)

Fig. 16b. shows the contour plot for effect of independent variables on D85. Based on Eq. 1, X dimension has positive effect for D85 response, whereas, drug loading has negative effect on D85.

Table 10. Analysis of Variance (ANOVA) for Statistical Analyses of D85

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1604.75	2	802.38	43.21	< 0.0001	significant
A-Drug load	79.70	1	79.70	4.29	0.0682	
C-X	1525.06	1	1525.06	82.13	< 0.0001	significant
Residual	167.11	9	18.57			
Cor Total	1771.87	11				

D85 Time taken for 85% of cumulative drug release

X mm dimension A (Factor 1) Drug load

Cor, correlation

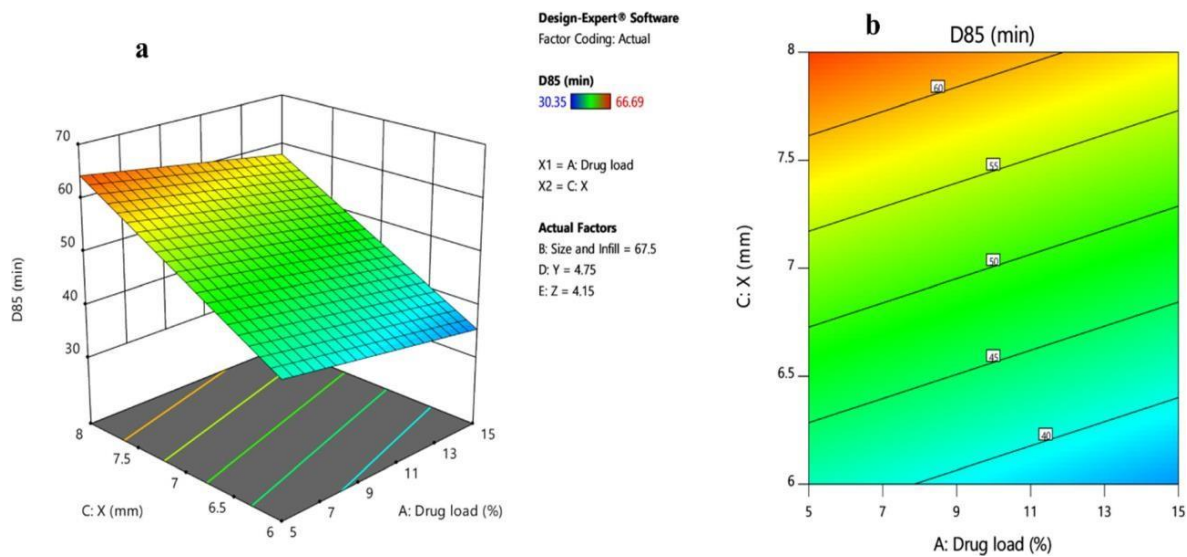


Fig. 16. a. Response surface plots of D85 and b. contour plot of D85.

4.4.10.2. Statistical analyses of responses %S_{ext}

As shown in Table 9, various responses were obtained for % S_{ext} by changing CQAs. ANOVA (Table 11) showed that model was significant ($p < 0.0001$). Values of coefficient of determination R^2 , adjusted R^2 , and predicted R^2 were 0.9544, 0.9283, and 0.8753, respectively. The predicted R^2 of 0.8753 was in reasonable agreement with adjusted R^2 of 0.9283. The model having difference of less than 0.2 between predicted R^2 and adjusted R^2 was good for prediction purpose. Irrespective of drug loading, higher amount of drug extraction was observed from SE compared to BE. Increase in % infill density from 45% to 90% resulted in reduced drug extraction from all the formulations. The following polynomial equation has been generated to establish the relation between CQAs and % S_{ext} as.

Actual Equation: %S_{ext} in 5min= +51.91583+0.237750*Drug load-0.330741*% infill density-6.47000*X+0.046407*(infill density*X)..... (2)

ANOVA (Table 11) analysis suggested that infill density has no significant effect (p value 0.6722) on % S_{ext} . Moreover, from Eq. 2 and ANOVA, drug loading has a positive and significant effect on % S_{ext} . X dimension has a negative but significant effect on response. Fig. 17b. shows the contour plot for effect of independent variables on % S_{ext} . As depicted in the contour plot, increased drug load resulted in increase in the amount of drug extracted. Whereas, increase in X dimension caused reduction in the amount of drug extracted. It was evident from contour plot that % infill density has no effect on % S_{ext} . Interaction graph of % S_{ext} versus infill density showed very interesting data. % S_{ext} was reduced with increase infill density in (X = 6 mm) small dimension egglet (SE) but opposite behavior was observed in egglet with bigger dimension (BE). Irrespective of drug loading, egglet with smaller dimension (SE) showed reduction in % S_{ext} with increase in % infill density.

Table 11. Analysis of variance (ANOVA) for statistical analyses of % S_{ext}

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	158.27	4	39.57	36.59	< 0.0001	significant
A-Drug load	11.31	1	11.31	10.46	0.0144	significant
B-Infill density	0.2107	1	0.2107	0.1948	0.6722	
C-X	133.67	1	133.67	123.62	< 0.0001	significant
BC	13.08	1	13.08	12.10	0.0103	
Residual	7.57	7	1.08			
Cor Total	165.83	11				

% S_{ext} in 5 min Percentage of drug extracted using water in 5 minutes

X mm dimension A (*Factor 1*) Drug load B (*Factor 2*) Infill density C

(*Factor 3*) X mm dimension

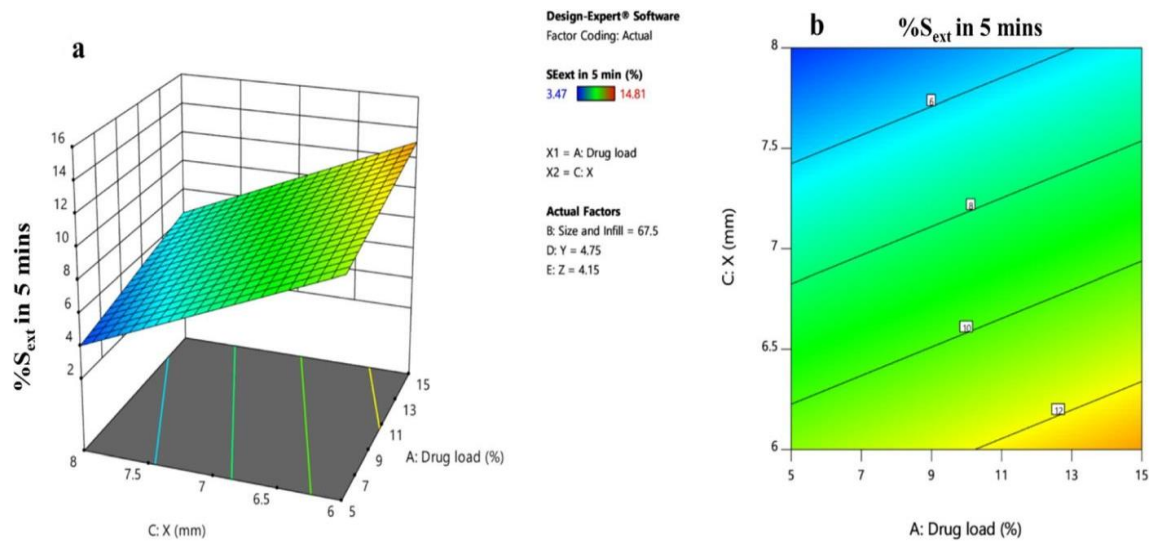


Fig. 17. a. Response surface plots of % S_{ext} and b. contour plot of % S_{ext}.

4.4.10.3. Optimization

After analyses of responses and development of proper regression models, optimization was done to select design space. Criteria were set for D85 and %S_{ext} to achieve shorter D85 and minimum % S_{ext}. To achieve these pre-set criteria with 95% confidence, the software suggested ranges of factors using desirability function. Further to confirm this, validation trials in triplicate were performed using SE of 5% w/w drug loading with 90% infill density. Results were found to be within 95% confidence interval of the predicted value (Table 12). Based on obtained design space, optimized setting of 15% w/w drug loading with 45% infill density in SE dimension was further selected for level 2 and level 3 extraction studies as per the USFDA guidance. Extraction studies employing level 2 and level 3 solvents were performed in triplicate.

Table 12. Results of confirmation trials

Response	Predicted Mean	Observed	n	95% PI low	95% PI high
D85	41.7946	39.21	3	34.0882	49.5009
% S_{ext} in 5 min	9.57792	8.68	3	7.39015	11.7657

D85 Time taken for 85% of cumulative drug release

% S_{ext} in 5 min Percentage of drug extracted using water in 5 minutes

4.4.11. Solvent Extraction in Level 2 and Level 3 Solvents

Optimized egglet showed < 30% and < 10% of drug extraction in 40% ethanol (level 2) and 100% ethanol (level 3), respectively. Moreover, the amount of drug extracted in acetone (level 3) was below the range of detectable limit. Very limited extraction of drug was attributed to PVA-based matrix. As per manufacturer's technical information, PVA (Parateck[®]MXP) has minimal or very limited solubility in ethanol and acetone (Corporation, 2016a).

5. Development of multi-dose oral abuse deterrent formulation of Loperamide using Hot melt extrusion

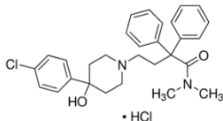
5.1. Introduction

5.1.1. Drug (Loperamide Hydrochloride)

Chemically loperamide is a derivative of phenylpiperidine, which is an opioid agonist. Initially classified in the US under a Schedule II, it was later shifted to a Schedule V in 1977; from 1982 it has not been identified as a controlled substance and is available OTC without a prescription. Pharmacologic effect is attained primarily by binding peripherally as a μ -receptor agonist on the mesenteric plexi of enteric wall. By administering in therapeutic doses (8mg/day) it reduces the gastrointestinal motility. Therapeutically, loperamide is used for treatment of diarrhea including traveler's diarrhea and gastrointestinal inflammation. Loperamide Hydrochloride drug profile was outlined in Table 13.

Table 13. Drug Information (Loperamide Hydrochloride)

(Adapted from Ben- Hander et al., 2015; Kasim et al., 2004; Kortejärvi et al., 2014)

Name	Loperamide hydrochloride
Chemical Name	4-(p-chlorophenyl)-4-hydroxy-N, N-dimethyl- α , α -diphenyl-1-piperidinebutyramide monohydrochloride
Molecular formula	$C_{29}H_{34}Cl_2N_2O_2$
Molecular weight	513.5 g/mol
Structure	
CAS No.	53179-11-6
Description	Phenyl piperidine derivative
Melting point	223-226°C
Partition coefficient	4.7
Solubility	0.00086 mg/mL in water
BCS class	Class IV
Dosage	Dose: 2mg – 8mg
Indication and use	Anti-Diarrheal drug

5.1.2. Abuse of novel psycho active substances (NPS)

Recently, the abuse of prescription drugs has been rising at a higher rate, causing greater threat to public health in the United states (Nukala et al., 2019b). Simultaneously, the deaths associated with the opioid epidemic is increasing during recent years (Miller et al., 2017). Due to the limited availability of prescription opioids and emergence of abuse deterrent formulations by the USFDA, the modern-day abusers have been shifting towards NPS (Schifano et al., 2018). A range of prescription (e.g. Pregabalin, Gabapentin etc.) and OTC drugs (e.g. Loperamide, Dextromethorphan etc.) were categorized as NPS's due to their scope of abuse from large doses, which yields intense psychoactive action and cannot be diagnosed in drug screenings (Schifano et al., 2018).

5.1.3. Abuse of Loperamide Hydrochloride

A perfect example is an OTC anti-diarrheal drug, loperamide. This OTC medication is gaining popularity as a drug of abuse for attaining euphoria and for amelioration of opioid withdrawal symptoms (Lasoff et al., 2017; Miller et al., 2017). Due to its ease of availability and very low price, loperamide, is gaining interest among many opioid abusers (Katselou et al., 2017). Numerous reports indicate loperamide to be alternative for opioids. Based on National Poison Database System (NPDS) between 2008 and 2016 there has been a significant increase in loperamide misuse with 179 reported cases. In addition, more than 50% reports were noted after January 1, 2014 (Miller et al., 2017). Between 2010 and 2015, the NPDS have reported a total of 1736 reports of intentional abuse (Borron et al., 2017; Wu and Juurlink, 2017).

5.1.4. Multidose oral abuse of Loperamide Hydrochloride/ Poor Man's Methadone

Loperamide is sold as a hydrochloride salt under the trade name Imodium[®]/A-D or in generic form as an anti-diarrheal drug (Katselou et al., 2017). It is available in forms of a tablet, capsule, and liquid at a recommended dose not exceeding 8 mg/day (nonprescription) or 16 mg/day (prescription) (Miller et al., 2017). After ingestion of 2 mg of loperamide HCl the plasma levels of drug remained under 2 ng/mL. Hence, it is regarded as safe for oral ingestion in therapeutic doses only. However, when ingested in elevated doses, it has been reported to alleviate the symptoms of opioid withdrawal by various drug use websites including drug forums online from 2005. Being a choice for drug of abuse due to its associated euphoric effects at larger quantities of 60 mg, it acts as a possible alternative to methadone, hence it is often regarded as “poor man’s methadone” (Daniulaityte et al., 2013; Katselou et al., 2017). Based on the USFDA report, loperamide abuse and misuse initiates, especially at doses of 60 mg (around 30 tablets) (Inc., 2016; Jaffe et al., 1980). In a survey an abuser reported to ingest an average amount of 70 mg to several hundred mgs (1600 mg) a day (Katselou et al., 2017; Wu and Juurlink, 2017). We have also referred to the experiences of loperamide abusers described on websites like bluelight, drugs forum, erowid (Katselou et al.,

2017; Wu and Juurlink, 2017). Loperamide has a low potential for central nervous system (CNS) effects when administered in therapeutic doses (Katselou et al., 2017). In the case of ingesting doses higher than recommended, it has an ability to permeate into the CNS which increases the half-life. The average elimination half-life ($t_{1/2}$) of loperamide was reported to be 10.8 hours, having a range of 7-15 hours. However, when overdosed the half-life increased to 41 hours (Wu and Juurlink, 2017). Normally it is unable to pass through the Blood brain barrier (BBB) and has poor bioavailability (0.3%), but in high doses it can induce effects on the CNS (Bruni et al., 2013; Katselou et al., 2017). Respiratory depression, cardiac dysrhythmia and vision impairment were found to be associated with supratherapeutic doses of loperamide (Lasoff et al., 2017).

5.1.5. USFDA plan of action to reduce loperamide Hydrochloride abuse

Recently on (January 30th, 2018), the USFDA recommended a safety prevention for the manufacturers to prepare blister packs or single dose packaging to limit the number of doses in a package (USFDA, 2018a). The USFDA urges patients to follow package instructions while using loperamide. In addition, the USFDA informs health care professionals to consider loperamide as a possible cause of cardiac events (USFDA, 2018b). Naloxone is commonly used to treat loperamide overdose. But to overcome the overdose toxicity activated charcoal is preferred, only if the patient's mental status is active (Katselou et al., 2017; Wu and Juurlink, 2017).

Thus, in this work, we have demonstrated the proposed concept. Two gastric pH soluble polymers Eudragit® EPO and Kollicoat® Smartseal 100P were investigated as acid soluble matrix in the preset work. Initially, LPH loaded filaments were prepared using pH sensitive (gastric pH soluble) polymers by HME. Amount of free base needed to raise the pH >5 in various media was evaluated. Tablets comprising of crushed extrudates and specific amount of base were prepared and characterized. *In vitro* dissolution of single and multiple tablets of Imodium® and SJU tablets were carried out in biorelevant media.

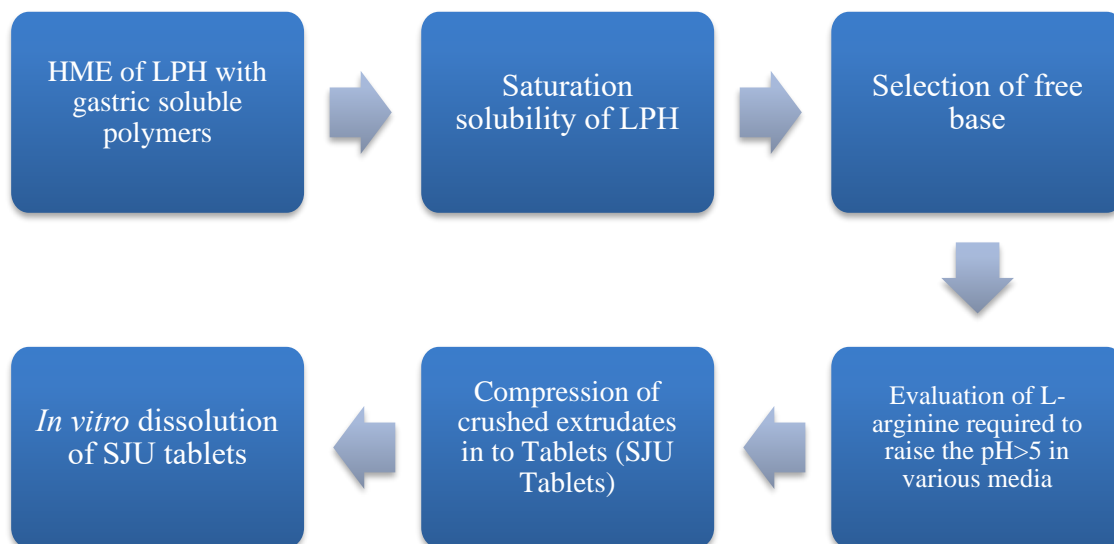


Fig. 18. Schematic diagram of proposed study (LPH).

5.2. Materials

Loperamide hydrochloride (LPH) was purchased from AK Scientific, Inc. (Union city, CA). Imodium[®] tablets were purchased from Rite Aid Pharmacy. Eudragit[®] EPO was generously gifted by EVONIK[®] (Parsippany, NJ). Kollicoat[®] Smartseal 100P and Kollidon[®] CL were kindly donated by BASF (Florham Park, NJ). L-arginine was purchased from Alfa Aesar (Tewksbury, MA). Avicel[®] PH 102 was obtained as a gift from FMC BioPolymer (Philadelphia, PA). Acetonitrile (HPLC grade) and salts (HPLC grade) for preparing buffer in mobile phase were purchased from Fisher Scientific Co. (Pittsburgh, PA). Biorelevant media ingredients lecithin, pepsin, sodium taurocholate, sodium chloride, hydrochloric acid was purchased from Fisher Scientific Co. (Pittsburgh, PA). All materials were used as received.

5.3. Methods

5.3.1. Analytical Method (HPLC)

The drug content analysis was done using Waters alliance system equipped with 2998 PDA (Photo diode array) detector and CortecsTMC18 column (4.6mm×50mm, 2.7μm). Chromatographic separation was achieved using a mobile phase consisting 5mMol Phosphate buffer (pH 3.5) and acetonitrile (ACN) (50:50, v/v). The flow rate was maintained at 0.25 mL/min with an injection volume of 5μL. Empower 3 software was used to monitor and process output signal. The column was maintained at room temperature (25°C) and detected at a λ_{max} of 219 nm. The retention time was found to be 4±0.5 minutes. For drug content analysis the following method was used; 100 mg samples (LPH loaded crushed filament) was accurately weighed and placed in 50 mL volumetric flask. This was followed by addition of 25 mL of ACN to volumetric flask and sonicated for 15 minutes. Later the volume was made up to 50 mL with 5 mMol phosphate buffer (pH 3.5) and continued sonication for an additional 30 minutes to obtain a clear homogenous solution. The resultant solution was subjected to filtration using 0.45μm syringe filters (nylon). The filtrates were loaded into HPLC vials for drug content analysis. All measurements were made in triplicate (n=3).

5.3.2. pH solubility profile

Saturation solubility of LPH was evaluated between pH 2 -10.5. Excess amount of LPH was added to each tube containing 3 mL of phosphate buffer pH 2, pH 4, pH 6, pH 7.5, pH 9, pH 10.5, respectively. After addition of LPH, the individual tubes were continuously stirred for 24 hours on a mechanical shaker maintained at 37°C. Following 24 hours of equilibration, the tubes were centrifuged at 6000 rpm for 10 minutes to obtain visually clear supernatants. Clear aliquots were withdrawn from each tube and filtered using 0.45µm syringe filters (nylon). The concentration of LPH in filtrate was analyzed using HPLC. All measurements were done in triplicate (n=3).

5.3.3. Hot melt extrusion of Loperamide Hydrochloride loaded filaments

Hot melt extrusion was carried out using 11mm parallel twin screw melt extruder (Process 11, Thermo Fisher Scientific, Waltham, MA) comprised of 8 electric heating zones with an L/D ratio of 40. For the preparation of LPH loaded filaments two different polymeric blends were prepared using Eudragit® EPO and Kollicoat® Smartseal 100P, respectively and extruded individually. LPH and each polymer were weighed accurately in a 1:49 weight ratio (2% w/w drug loading) and thoroughly mixed in a Turbula® mixer (Willy A. Bachofen, Switzerland) for 30 minutes to obtain homogenous blend. The resultant homogenous mixtures were fed to heated melt extruder at a feeding rate of 2 g/min and processed at 150°C (individual zone temperatures were summarized in Table 14), by maintaining a die temperature of 160 °C and extruded using a circular 2.0 mm die with 250 rpm screw speed. Three screw designs of extruder were evaluated for processing the drug polymer homogenous mixture. Ludovic® simulation software (Saint-Etienne, France) was used to demonstrate the three screw configurations as shown in Fig. 19. First screw design (SDA), second screw design (SDB) and third screw design (SDC) were designed to have three (K_A1 , K_A2 , K_A3), two (K_B1 , K_B2) and one kneading zones (K_C1). Every screw design possessed conveying zones in addition to a kneading zone. The screw

design for HME along with processing temperatures was selected based on torque analysis and physical appearance of extrudates. The extruded filaments were placed and properly sealed in plastic bags and stored at room temperature before subjected to milling.

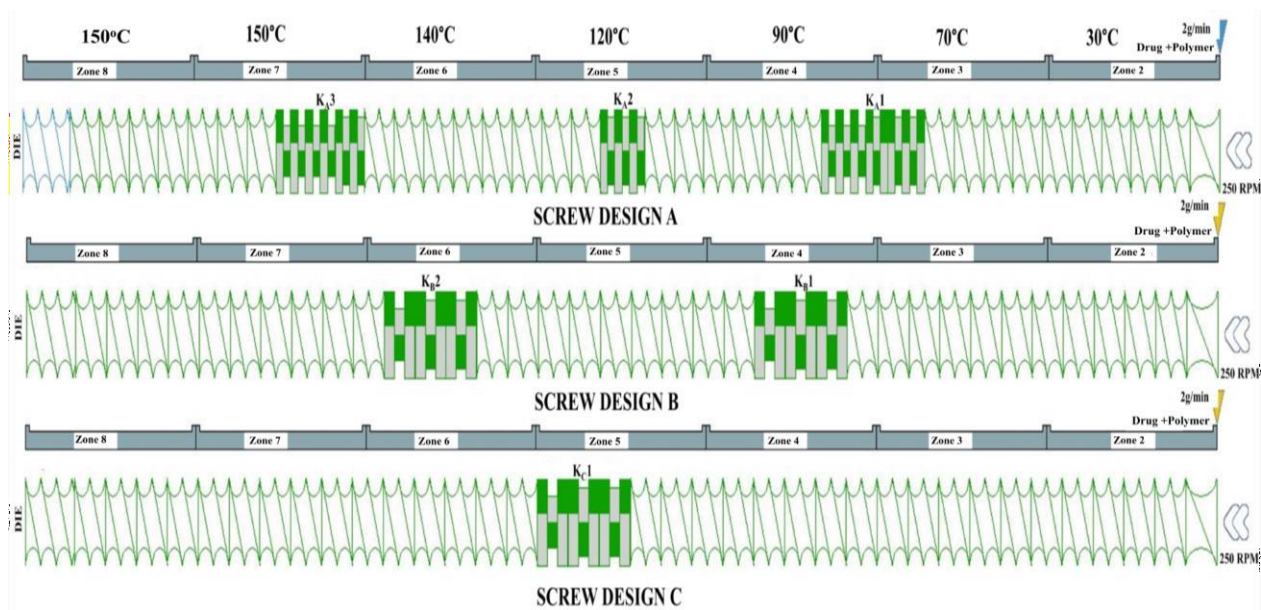


Fig. 19. Three screw designs (SDA, SDB, SDC) of Hot melt extrusion. Lower shear screw design (SDC) was found to be most suitable for extrusion.

Table 14. HME heating zones and associated temperatures respectively.

Zone #	Temperature °C
Zone 1(feeding zone)	25 (room temperature)
Zone 2	30
Zone 3	70
Zone 4	90
Zone 5	120
Zone 6	140
Zone 7	150
Zone 8	150

5.3.4. Thermogravimetric analysis

Thermogravimetric analysis (TGA) was performed to evaluate the thermal stability using a thermogravimetric analyzer, TGA Q50 (TA Instruments, Newcastle, Delaware, USA). TGA studies were done according to literature (Palekar et al., 2019). Pure LPH, neat polymers Eudragit® EPO, Kollicoat® Smartseal 100P, individual physical mixtures and crushed filaments were used for TGA. Samples of about 5 mg were accurately weighed and placed on a tared platinum pan. Prior to analysis, samples were held for one minute at 30 °C under nitrogen purge. During analysis, the temperature ramp was operated at a rate of 5 °C/min. The percentage weight loss from individual samples was determined by heating from 30 °C to 300 °C under a constant nitrogen purge of 20mL/min. The obtained data was analyzed using TA instruments universal analysis 2000 software.

5.3.5. Solid state characterization

Solid-state characterization of pure LPH, neat polymers Eudragit[®] EPO, Kollicoat[®] Smartseal 100P and their associated physical mixtures of drug and polymer along with crushed filaments was carried out using differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD).

5.3.5.1. Differential scanning calorimetry

DSC thermograms of samples were generated using a Q200 modulated DSC instrument (TA Instruments, New Castle, Delaware, USA) as per the literature (Nukala et al., 2019b). About 5 mg of samples were accurately weighed and placed in a Tzero[®] aluminum pans which were hermetically sealed. The experiments were conducted under a continuous nitrogen purge at a flow rate of 50 mL/min. For initial 5 minutes, the samples were equilibrated at 25°C. Later, the samples were subjected to heating from 25°C to 250°C at a heating rate ramp of 5°C/min along with modulation of 1°C/min. The collected data was analyzed using TA instruments universal analysis 2000 software. The temperature scale of instrument was calibrated using Indium as standard.

5.3.5.2. X-ray powder diffraction

Samples were characterized by X-ray powder diffraction (XRPD) using Shimadzu 6000 X-ray diffractometer (Shimadzu Corporation, Kyoto, Japan) based on literature (Nukala et al., 2019b). Before obtaining diffraction patterns, the sample specimens for the XRPD analysis were prepared by placing samples on a metal sample holder with cavity, followed by pressing the material to obtain smooth and uniform surfaces. Samples were analyzed through a CuK α , monochromatic radiation source emitting X-ray radiation with generated voltage of 40 kV and current of 30 mA respectively at room temperature. The diffraction patterns of samples were obtained by scanning over a continuous 2θ range of 10° – 40° at a rate of 2° /min using a 0.02° step size.

5.3.6. Selection of free Base

Commonly used alkalizing agents (Magnesium hydroxide, Calcium carbonate, sodium bicarbonate, L-arginine) were evaluated to find out the minimum amount for raising the pH > 5 in 250 mL of FaSSGF. 250 mL of media was based on realistic volume of fasted state in humans after assuming administration of drug product with 8oz (glass) of water.

5.3.7. L-arginine titration

Amount of base (L-arginine) required to increase the pH>5 in various solutions was determined by titrating L-arginine solution against various media. Initially stock solution of 100 mg/mL of L-arginine was prepared in water. The L-arginine solution was titrated with 250 mL of biorelevant media - Fasted state simulate gastric fluid (FaSSGF). 250 mL of media was based on realistic volume of FaSSGF after assuming administration of drug product with 8oz (glass) of water (Fiolka and Dressman, 2018; Food and Administration, 2017; Mudie et al., 2014). Usually in some severe cases abusers consume commonly available fluids like grapefruit juice (interacts with metabolism of LPH), aerated drink and beer along with drug to get high. By considering these severe cases, the additional titrations were performed by incorporation of 12 oz aerated drink, 4 oz grapefruit juice, 12 oz beer to 250 mL of FaSSGF respectively. Change in pH was constantly monitored during titrations. Volume of L-arginine solution was noted to calculate amount of L-arginine required to raise pH of FaSSGF above 5. FaSSGF was prepared with the protocol mentioned by (Otsuka et al., 2013). Composition of FaSSGF is summarized in Table 15.

Table 15. Composition of Fasted State Simulated gastric fluid
(Adapted from Otsuka et al., 2013)

Ingredients	FaSSGF
Lecithin (mM)	0.02
Sodium taurocholate (mM)	0.08
Pepsin (mg/mL)	0.1
Sodium chloride (mM)	34.2
Hydrochloric acid (mM)	25.1
pH	1.6

5.3.8. Tableting

LPH loaded filaments were milled using laboratory analytical mill and passed through series of sieves # 40, #60, #80 and #120 using a sieve analyzer (CSC Scientific, Fairfax, VA) at a vibration of 2mm amplitude for 10 minutes. The powder passed through sieve #40 and retained on sieve #60 was further used for tablet preparation. The composition of tablet blend is mentioned in Table 16. The tablet blend was mixed thoroughly in a Turbula[®] mixer (Glen Mills, Clifton, NJ) for 30 minutes prior compression. Tablets were compressed at pressure of 3000 lbs using flat face punches of 8 mm diameter (Natoli Engineering, Saint Charles, MO) on a single punch Carvar press assembly (Carvar Inc.). The die-wall was cleaned and pre-lubricated with magnesium stearate before each compression. The tablet blend was hand filled into the die before compression. Tablets compressed using Eudragit[®] EPO based filaments and Kollicoat[®] Smartseal 100P based filaments were labeled as SJU1 and SJU2, respectively.

Table 16. Formulation composition of tablet (each weighs 275 mg)

Ingredients (mg)/tablet	SJU1/ SJU2
Milled filaments	100
Avicel® PH102	50
L-arginine	100
Kollidon® CL	25

#SJU1 = Crushed filaments of LPH loaded Eudragit® EPO;

SJU2 = Crushed filaments of LPH loaded Kollicoat® Smartseal 100P

5.3.9. Physical characterization of Loperamide Hydrochloride Tablets

Tablets were evaluated for thickness, diameter, weight variation, hardness and friability. For testing the weight variation 20 different tablets were selected and weighed on an electronic balance (Sartorius, Gottingen, Germany). Friability test was performed using a HT-2 Friabilator USP (Sotax, Switzerland). Randomly selected tablets (n = 10) were preweighed and placed inside the friabilator and rotated at a speed 25 RPM for 4 min as per USP. Later, the tablets were reweighed, and the percentage weight loss was calculated. Pharmaceutical hardness tester (Pharma Alliance group CA, USA) was used for testing the tablet hardness. The tensile strength of tablets was calculated using the tablet breaking force and measured dimensions as per the standard procedure given by Fell et al (1970) (Fell and Newton, 1970). All hardness and tensile strength measurements were done in triplicate (n=3).

5.3.10. *In vitro* drug release

5.3.10.1. Single unit dissolution

In vitro drug release was carried out in 250 mL of FaSSGF using USP II dissolution apparatus (Symphony 7100, Distek, New Brunswick, NJ). The dissolution medium was maintained at $37\pm0.5^{\circ}\text{C}$ and stirred at 50 rpm paddle speed. Single unit dissolution study was carried out for Imodium[®], SJU1 and SJU2 tablet individually. Samples (4 mL) were withdrawn at predetermined time intervals of 5, 10, 15, 20, 30 and 45 minutes. At each time point, equal volume of fresh dissolution medium (maintained at 37°C) was replaced into the dissolution vessels. Withdrawn samples were filtered through $0.45\mu\text{m}$ syringe filters (nylon) and filtrates were analyzed for drug content using HPLC.

5.3.10.2. Multi-unit dissolution

To evaluate deterrence to multi dose abuse, dissolution study with multiple tablets was carried out. This study was conducted by adding multiple tablets in the dissolution vessel at a time. 15 tablets of Imodium[®], SJU1 and SJU2 tablets added to each dissolution vessel. Samples were collected at predetermined time intervals as mentioned in single unit dissolution. Similar to single unit dissolution, fresh dissolution medium was added at every time point. The collected samples were filtered using 0.45µm syringe filters (nylon). Drug release at various time intervals was analyzed through HPLC. All dissolution studies (single and multi-unit) were carried out in triplicate (n=3).

The formulation (SJU1 or SJU2) which will be able to obtain immediate release in single unit dissolution and negligible release in multi-unit (#15) dissolution will be selected for further studies. Next, optimized formulation (SJU Tablet) will be used for multi-unit dissolution with 30 tablets (mimic the conditions of abuse). Further the optimized formulation with single unit will be evaluated for drug release in various biorelevant media like FeSSGF, FaSSIF, FeSSIF. Finally step dissolution will be carried out for optimized formulation by taking single unit only.

Schematic presentation of proposed technology and experimental “proof of concept” is given in Fig. 20.

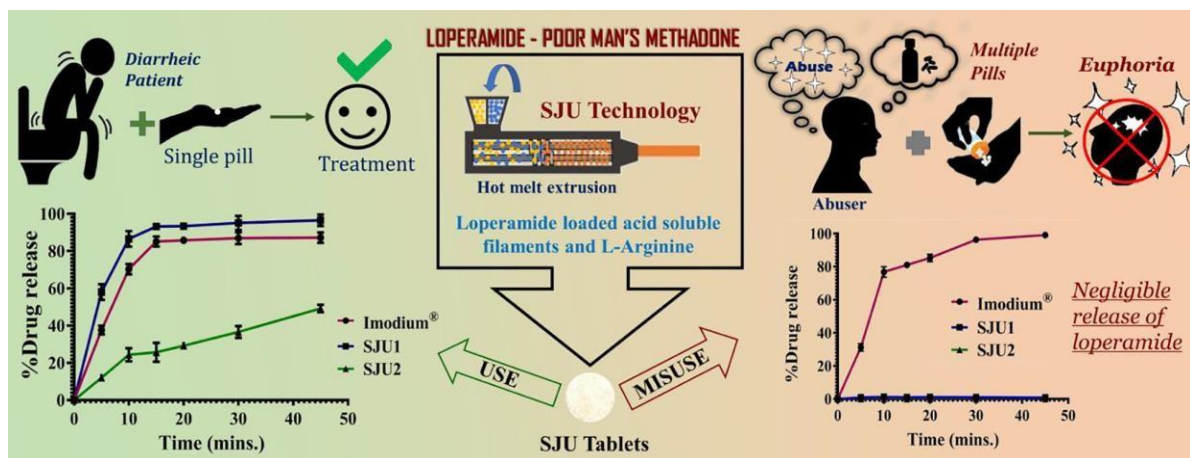


Fig. 20. Schematic diagram for the development of multi-dose oral abuse deterrent formulation of loperamide using Hot melt extrusion.

5.4. Results and Discussion

5.4.1. Analytical Method (HPLC)

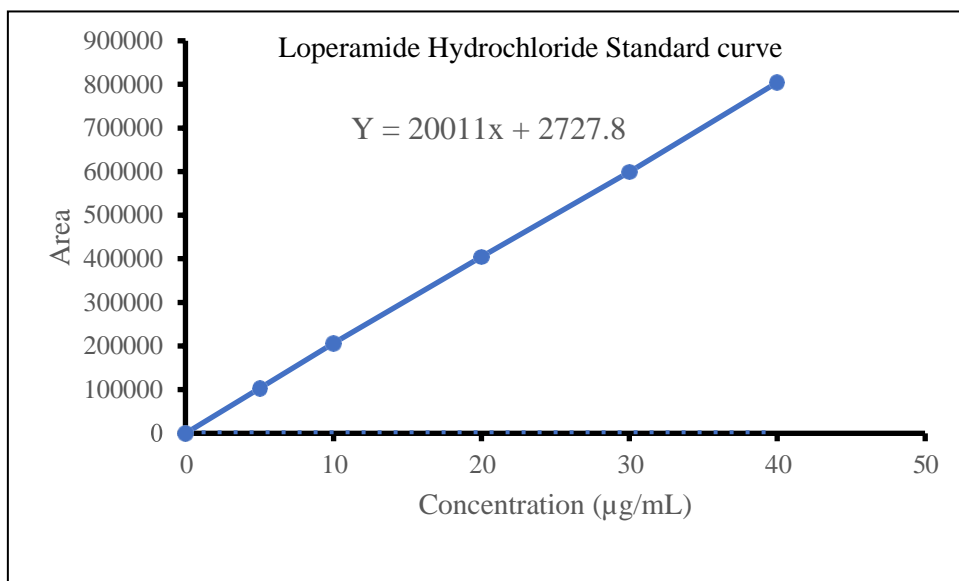


Fig. 21. Standard curve of Loperamide HCl.

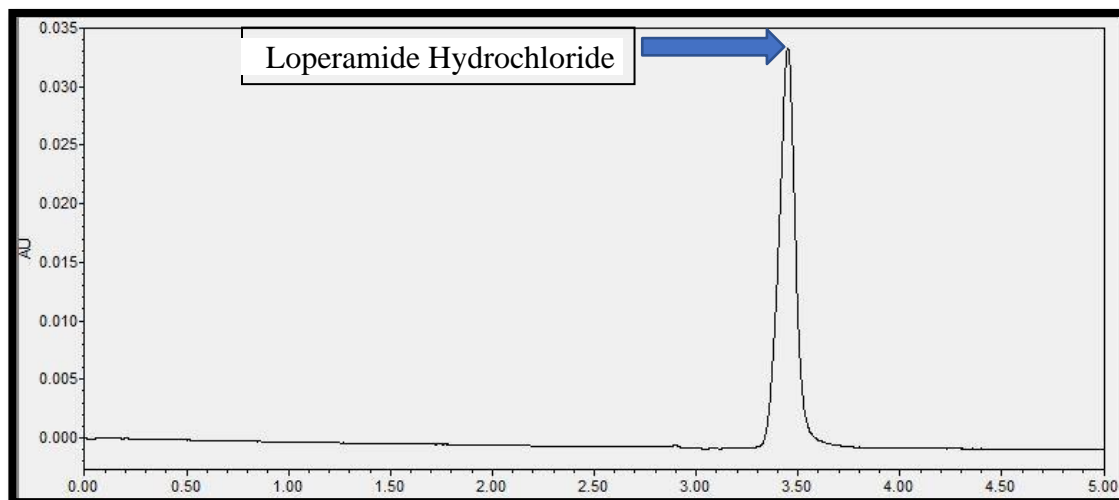


Fig. 22. HPLC chromatogram of Loperamide HCl.

5.4.2. pH solubility study

LPH showed pH dependent solubility which is attributed to basic nature of LPH. As shown in Fig. 23, pure LPH has a solubility of 1.02 mg/mL, 0.37 mg/mL and 0.1 mg/mL at pH 2, 4 and 6, respectively. Further increase in pH resulted in marked decrease in solubility to 0.02 mg/mL at pH 7.5. Thus, nearly 20-fold reduction in solubility was observed at neutral to slightly alkaline pH. No detectable solubility was observed at pH 10.5. Our observation was in accordance with Bruni et al (2013) (Bruni et al., 2013).

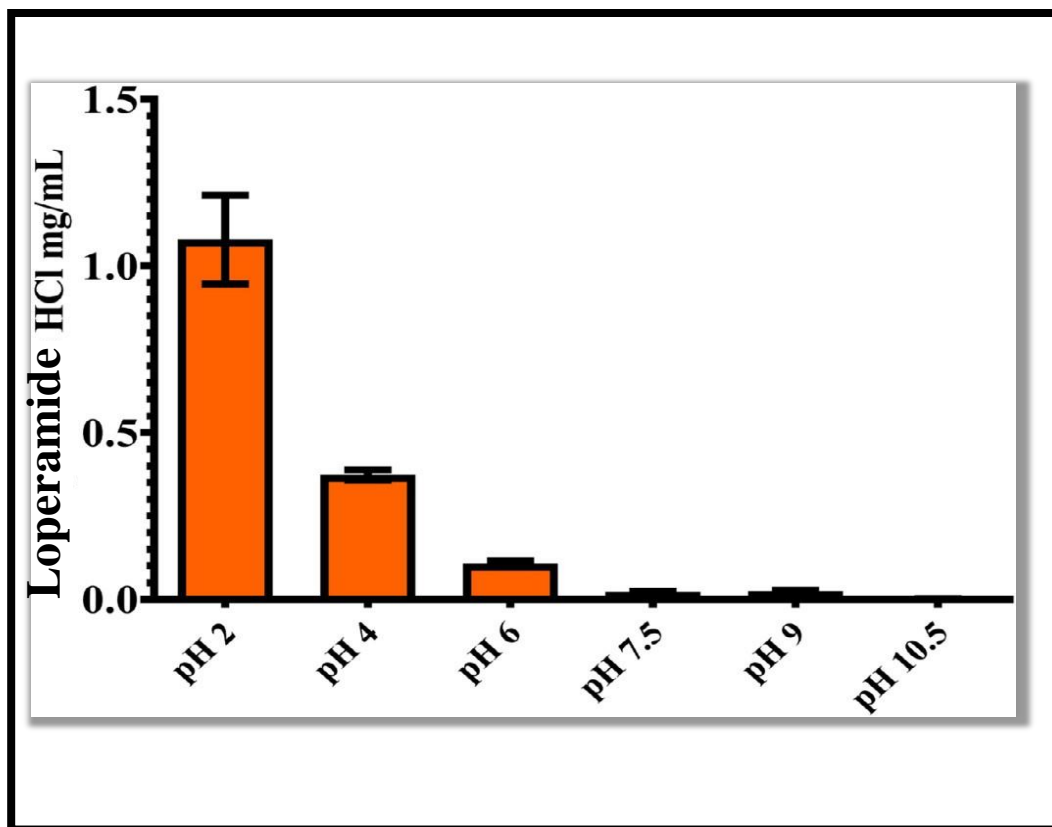


Fig. 23. Solubility of Loperamide Hydrochloride at various pH (n=3). Loperamide hydrochloride exhibited decreased solubility with increase in pH.

5.4.3. Hot melt extrusion of Loperamide Hydrochloride loaded filaments

Three screw designs were evaluated for extrusion. Extrusion was carried out at 150°C that is above the glass transition temperature (T_g) (52°C) and below the degradation temperature (T_d) (250°C) for Eudragit® EPO. The processing temperatures for extrusion of Eudragit® EPO was in well accordance with literature (Parikh et al., 2016). The torque generated during extrusion was monitored. As reported in Fig. 19, Extrusion with screw design - SDA (3 kneading zones (high shear)) resulted in sudden increase in torque (>90%) which led to automatic shutdown of extruder. Thus, impeding the flow of drug polymer mixture through the extruder. Similarly, second screw design (SDB) with two kneading zones (medium shear) resulted in high torque (>80%) causing extruder to cease. With screw design SDA and SDB the material was not melted properly resulting in solidification of components and blocking the path/channel. Interestingly, third screw design (SDC) with only one kneading zone (low shear) generated a torque of <60% ($30\pm 5\%$) thus allowing the molten material to pass/flow throughout the length of extruder. Thus, SDC was used for further study.

The design of the screw configuration/geometry of screws play a key role in processing the material through extruder (Crowley et al., 2007). Mainly, the alignment of screw elements permits the continuous flow of material through the extruder body.

Broadly two types of screw elements conveying, and kneading/mixing elements were used in extrusion process. Movement of material inside extruder possible through rotation of screws imparting shear and thermal energy on the material along with assisted heating zones. Conveying elements are responsible for conveying whereas, kneading elements are for mixing. The primary role of kneading elements is dispersive mixing, where the material gets captured locally in a pressurized region and gets squeezed. Kneading elements arranged in a series with different offset angles (forward) generates varied levels of shear depending on construction. Reducing the number of kneading elements decreases the intensity of mixing the material. By operating with initial design (SDA) the material (low T_g 52°C) might turned to a rubbery state before reaching the first kneading zone (K_{A1}) (in between zone 3 and 4). This can be attributed to the increase in temperature from 30°C (zone 2) to 70°C (zone 3). K_{A1} composed of 14 kneading elements aligned with progressive offset angles (0°-90°-0°-90°-0°-90°-0°-90°-0°-60°-120°) forward. This kind of increase in number of kneading blocks with higher degree of offset angle provides more shear. Thus, K_{A1} imparts additional shear causing processed material to get trapped and squeezed between screws. Due to the gradual increase in temperature and alignment of kneading blocks, the rubbery material got stuck in between screws of K_{A1} , thus restricting the further movement of screws.

This phenomenon resulted in blockage of the channel and triggering of torque. Hence, in a summary, the material was not mixed properly (material was not completely molten) due to its rubbery state and high shear of design causing increase in torque. In SDB the initial kneading zone (K_{B1}) was present in zone 4 (90°C) with 9 kneading elements ($0^\circ-60^\circ-120^\circ-0^\circ-60^\circ-120^\circ-0^\circ-60^\circ-120^\circ$) having offset angles forward. However, even when attempted with SDB the conveyed material became rubbery in between zone 2 (30°C) and zone 3 (70°C) before entering K_{B1} in zone 4. Due to higher temperature of 90°C in zone 4, the material turned slightly molten when compared to nature of material in between zone 3 and 4 of SDA. Yet, the induced degree of molten nature was not considered enough for getting conveyed further from K_{B1} due to high imparted shear on material. So, it caused blockage of channel by getting trapped in between the screws of K_{B1} , because of incomplete solidification. Whereas, by employing SDC majority of the fed material turned to melted state prior reaching (K_{C1}) with 9 kneading elements ($0^\circ-60^\circ-120^\circ-0^\circ-60^\circ-120^\circ-0^\circ-60^\circ-120^\circ$) with offset angles forward in zone 5 (120°C). The configuration of kneading elements in SDC was designed to have a low shear. Hence, progressive increase in temperature (30 °C-70°C-90°C-120°C) led to sufficient melting of mixture and proper mixing within kneading elements (K_{C1}), thus facilitating the passage of mixed material through channel to end

of extruder. SDC was chosen as an optimized design for processing as it was able to produce clear extrudates. In some instances, the changes in configuration of screw elements help in melting, processing of materials properly and improving the flow through the extruder (Crowley et al., 2007). Consequently, SDC was selected further for extruding LPH loaded filaments using Eudragit® EPO and Kollicoat® Smartseal 100P individually. Novel polymer Kollicoat® Smartseal 100P has a T_g of 50°C (similar to Eudragit® EPO) hence the choice of using SDC has been warranted. Fig. 24. Plot indicated the % torque at different temperature for three screw designs.

HPLC analysis of crushed extrudates of Eudragit® EPO and Kollicoat® Smartseal 100P revealed that drug content in both extrudates was found to be $>98\% \pm 1.5$. It means that drug is uniformly dispersed in the filaments and did not degrade.

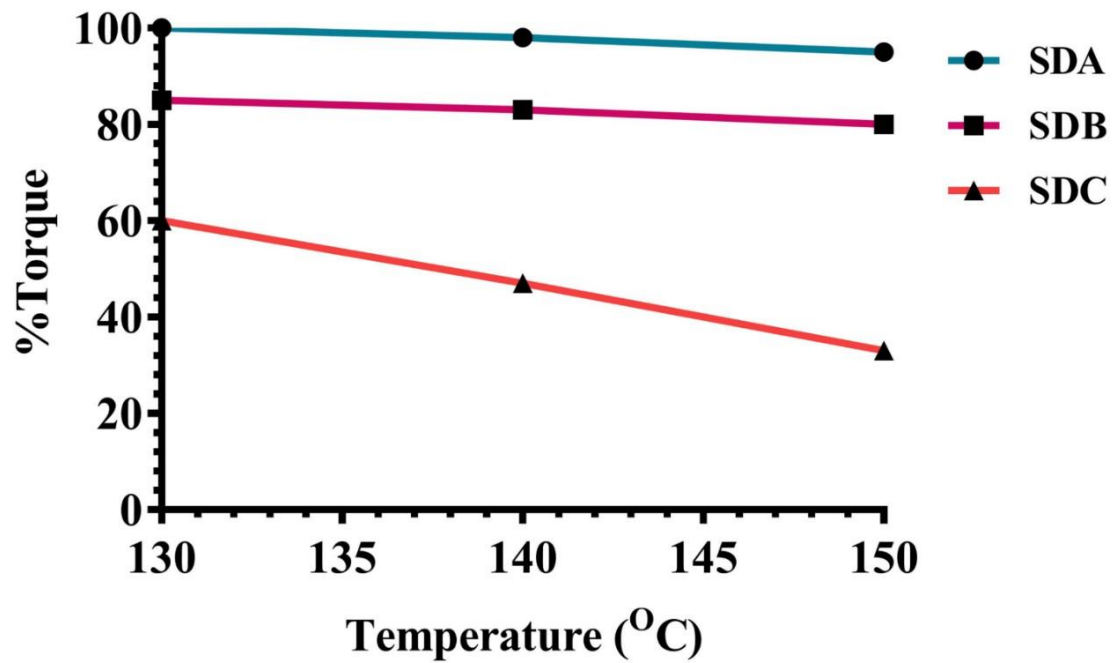


Fig. 24. %Torque analysis at different temperatures for the three screw designs SDA, SDB, SDC. It was observed that SDC was optimum for extrusion based on % Torque analysis.

5.4.4. Thermogravimetric analysis

TGA was performed to evaluate the thermal stability of LPH and polymers to access their stability during hot melt extrusion. Fig. 25, illustrates the thermogravimetric analysis for LPH, polymers, physical mixtures and crushed filaments. LPH showed a negligible mass loss at temperatures $<250^{\circ}\text{C}$ followed with a rapid mass loss at temperatures $>250^{\circ}\text{C}$. There was no significant decrease in the % weight with an increment in temperature. It can be observed that over the course of the analysis, Eudragit[®] EPO and Kollicoat[®] Smartseal 100P exhibited a high thermal stability up to 200°C . Our results were in good accordance with literature reports (Liu et al., 2013; Porfiryeva et al., 2019). Similarly, crushed filaments from both polymers showed thermal stability up to 200°C . Altogether, TGA studies determined that the temperature for hot melt extrusion of 150°C was suitable for the processing.

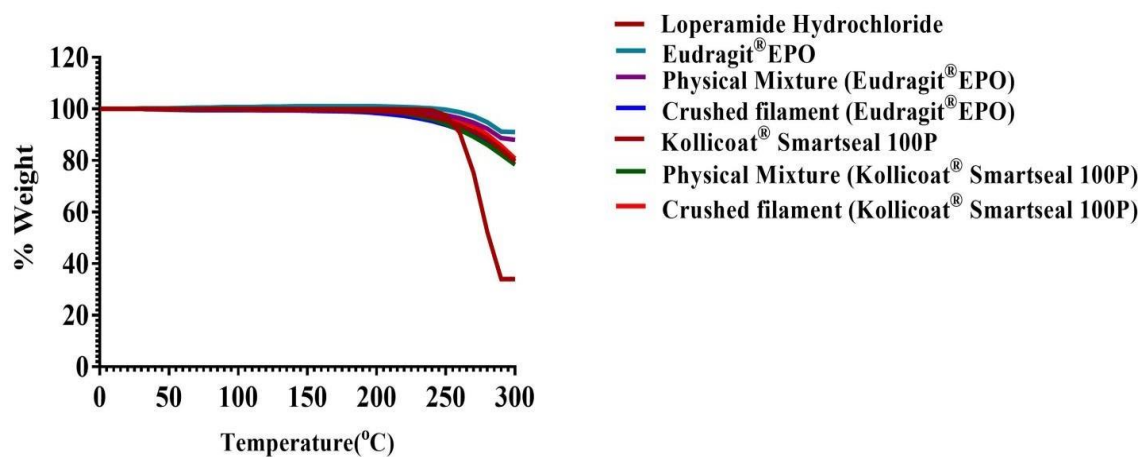


Fig. 25. Thermogravimetric analysis. LPH demonstrated thermal stability up to 250°C.

Crushed filaments and neat polymers exhibited thermal stability up to 200°C.

5.4.5. Solid state characterization

DSC thermograms of LPH showed a sharp peak at 225°C corresponding to crystalline nature of drug (Fig. 26A). Our observation was in accordance with Bruni et al (2013) (Bruni et al., 2013). Glass transition temperatures (T_g) of Eudragit® EPO and Kollicoat® Smartseal 100P were 52°C and 50°C, respectively. In either of the physical mixtures the characteristic melting endotherm for LPH was not visible. This is due to low LPH content (2% w/w) and it was insufficient to generate an endotherm. Crystalline peak of LPH was absent in crushed filaments. However, based on DSC results solid state of LPH in filament is difficult to predict because of absence of LPH endotherm in physical mixture itself. XRPD diffraction patterns were reported in Fig. 26B. X-ray diffractogram of pure LPH revealed 2-theta characteristic predominant crystalline peak at 16.52° along with some crystalline peaks of lower intensity at 13.14° and 18.7°. Our results were in accordance with Woertz et al 2015 (Woertz and Kleinebudde, 2015). Furthermore, XRPD patterns of physical mixtures revealed a crystalline peak of very low intensity at 16.5° (indicating LPH) with a broad halo in majority of diffractograms. However, the lower intensity of peak was because of low amount of LPH in both mixtures. Interestingly, crushed filaments of both polymers did not show any LPH peak which confirmed that LPH is in

molecularly dispersed state. In case of Eudragit® EPO and Kollicoat® Smartseal 100P the XRPD patterns exhibited a typical amorphous halo region for both polymers (Li et al., 2016). Moreover, filaments were very clear and transparent after extrusion which also confirmed that LPH is homogenously and molecularly dispersed within filament. Our observation was in accordance with previous reports (Genina et al., 2013). Hot melt extrusion is widely reported in literature to generate molecular dispersion of drug within polymer (Sarode et al., 2013). Amorphization or molecular dispersion of drug within filament is very important for long term stability of hot melt extrudates (Patil et al., 2016).

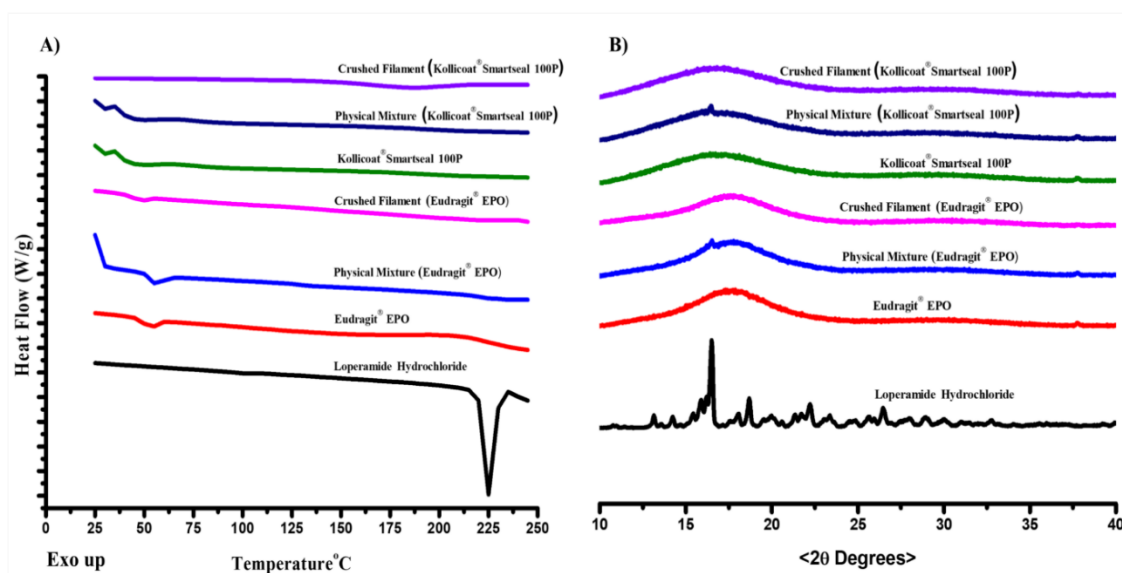


Fig. 26. Solid state characterization A) Differential scanning calorimetry B) X-ray powder diffraction. Absence of characteristic melting endotherm (26A) and disappearance of sharp crystalline peaks (26B) in both the crushed filaments indicated LPH was molecularly dispersed in polymer after extrusion.

5.4.6. Selection of free base

The amount required in raising the pH >5 for various alkalizing agents has been summarized in Table 17. Based on the shortest time required to raise the pH>5 L-arginine was selected for further studies. Because rest of the alkalizing agents required more >3 minutes in increasing the pH. Raising the pH rapidly (in < 1 minute) is of very pivotal to render the polymeric matrix insoluble and to retard the drug release.

Table 17. Time required for various alkalizing agents to raise the pH>5

Alkalizing agent	Amount (mg)	Time (Sec.)
Magnesium Hydroxide	200	>1200
Calcium Carbonate	400	>1800
Sodium Bicarbonate	1000	210 \pm 30
L-arginine	1200	8 \pm 2

5.4.7. L-arginine titration

Amount of L-arginine required to raise the pH >5 in various media is shown in Fig. 27. About 1.2 ± 0.2 gm of L-arginine was required to raise the pH FaSSGF from 1.6 to 5. We further estimated the amount of L-arginine required to raise the pH of FaSSGF mixed with fluid commonly consumed by abusers. After addition of aerated drink to FaSSGF the initial pH of mixture was 1.9 and it required 1.6 ± 0.1 g of L-arginine. Similarly, in case of beer the pH of mixture was 2.7 and it required 1.5 ± 0.2 g of L-arginine. Co-administering grapefruit juice has been reported to enhance the LPH associated euphoria. Some abuser's ingest grapefruit juice with LPH due to CYP3A4 inhibitory effect of grapefruit juice (Alexander et al., 2014; MacDonald et al., 2015). It results in enhanced oral bioavailability of LPH.

Therefore, titration was also carried out by adding 4 oz of commonly available grapefruit juice in to FaSSGF (initial pH 2.7). It required 2.7 ± 0.3 g of L-arginine to raise the pH >5. We selected L-arginine as a base to raise the pH because it's a non-essential amino acid that is consumed by humans in a regular diet (Wu et al., 2013). Daily acceptable dietary intake of L-arginine is about 20 g/day (Shao and Hathcock, 2008). It is also a major ingredient of many OTC multivitamin supplements. In any aforementioned conditions of abuse, the amount of L-arginine needed to raise the pH

remained within the limit of average daily (20 g/day) intake. Based on results of this study, we decided to use the amount of L-arginine in each tablet.

As mentioned previously, concept is to completely resist the release of drug from a polymeric matrix in case of multi-dose oral abuse. We decided to add, 100 mg in each tablet. So, when a diarrhea patient consumes 1-2 tablets, it will not change the pH of stomach. So, we can achieve complete solubilization of Eudragit[®] EPO and Kollicoat[®] Smartseal 100P and thereby complete LPH release. On the other hand, on consumption of 15 or more tablets at the same time, amount of L-arginine in the stomach will be increased to 1.5 g or higher. It will raise the pH of stomach to >8.5 as per our study. At this pH both the polymers are insoluble and as a result LPH will not be released from polymeric matrix.

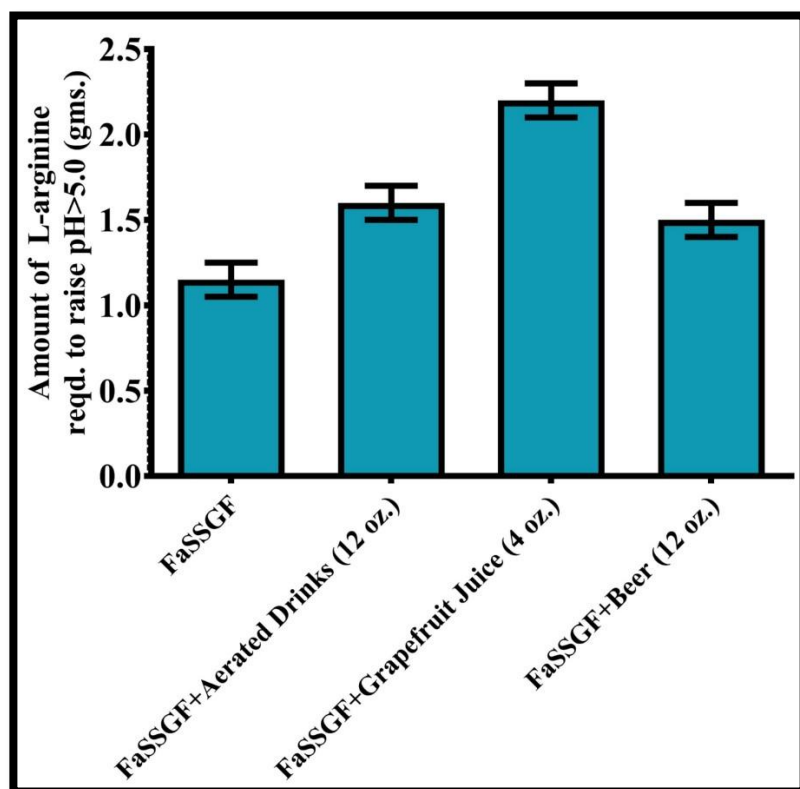


Fig. 27. Titration of L-arginine in 250mL of biorelevant media (FaSSGF) and 250 mL of FaSSGF with Aerated drink (12oz.), Grapefruit juice (4oz.), Beer (12 oz.), respectively (n=3). FaSSGF: Fasted state simulated gastric fluid. Amount of L-arginine required to raise pH>5 various types of media were found to be well within the limit of daily recommended intake (20 g/day).

5.4.8. Tableting and physical characterization of tablets

The target loading of LPH in each tablet was 2 mg (equivalent to strength of marketed Imodium[®] tablets with inactive ingredients like Lactose, cornstarch, talc, and magnesium stearate). Ten randomly selected tablets each from SJU1 and SJU2 weighed on an average of $275 \text{ mg} \pm 2 \text{ mg}$, thus ensuring uniformity in weight. Friability was found to be lower than 1% in both cases. Thus, confirming the mechanical stability of tablets. Hardness of tablet was $145 \pm 6.41 \text{ N}$ and $86 \pm 5 \text{ N}$ for SJU1 and SJU2, respectively. While tensile strength of tablets was $2.43 \pm 0.11 \text{ MPa}$ and $1.43 \pm 0.18 \text{ MPa}$ for SJU1 and SJU2 tablet when compressed at a pressure of 3000 lbs. Overall, SJU1 and SJU2 tablets meet the specifications described in manufacturing classification system (Leane et al., 2015).

5.4.9. *In vitro* dissolution

5.4.9.1. Single unit dissolution

The dissolution data is presented in Fig. 28. Volume of 250 mL was used based on a) matching realistic volume to simulate the total fluid present in stomach for dissolving dosage forms during gastric residence state. Along with the fluid after administration in the fasted state making it around 250 mL (Vertzoni et al., 2005). b) Assuming administration of dosage form in healthy humans by co administration with 8 fluid ounces of water (Fiolka and Dressman, 2018; Food and Administration, 2017). It was observed that both the tablets Imodium[®] and SJU1 exhibited >85% of drug release in 15 minutes. Thus, SJU1 met the criteria for immediate release tablet. Dissolution profile of SJU1 and Imodium[®] was found to be same. However, SJU2 showed only 25% of drug release in 15 mins. SJU2 demonstrated poor drug release of <50% in 45 minutes as shown in Fig. 28A. Slower dissolution characteristics of Kollicoat[®] Smartseal 100P compared to Eudragit[®] EPO could be responsible for slower and sustained release of LPH from SJU2.

5.4.9.2. Multi-unit dissolution

For evaluating the multidose oral abuse, the dissolution test has been performed by placing multiple tablets at once in dissolution vessel. Number of tablets was based on L-arginine titration plot in various media (Fig. 27). Dissolution profile of 15 tablets of Imodium[®], SJU1 and SJU2 in 250 mL of FaSSGF is given in Fig. 28C. Commercial Imodium[®] tablets exhibited 90% of drug release in 30 minutes (Fig. 28C). Most interestingly, SJU1 and SJU2 were able to resist the drug release (Fig. 28C). Both groups showed <5 % LPH release which confirmed that multi-unit abuse of LPH can be prevented by SJU1 and SJU2. Pictures of dissolution jar of SJU1 single unit and multiple unit after 45 minutes of dissolution study are shown in Fig. 26B and Fig. 26D respectively. Dissolution jar of single unit SJU1 showed absence of any extrudate particles, indicating complete solubilization of LPH loaded Eudragit[®] EPO extrudates. Off-white particles in the jar were from microcrystalline cellulose. On the other side, dissolution jar of multi-unit SJU1 dissolution study contained many extrudates (pale yellow in color) that are not solubilized as shown in Fig. 28D. Further, we also plotted the amount of LPH release vs time from multi-unit dissolution study. From Fig. 29, it can be inferred that about 27 mg of drug was released from Imodium[®] within 30 minutes. Theoretically, 15 tablets of Imodium[®] should have 30 mg LPH. Thus, a person

consumes multiple tablet of Imodium[®], proportionally high amount of LPH will be available for absorption. It's worthy to note that, less than 1 mg of drug was released from SJU1 and SJU2 tablets throughout the dissolution. This observed difference of phenomenon might be due to increased pH in multi dose dissolution (more L-arginine) thus rendering the filaments insoluble and reducing drug release. Hence, this study demonstrates the ability of SJU1 and SJU2 formulations to withstand the drug release in comparison with Imodium[®] in multi-unit dissolution (mimicking multidose oral abuse).

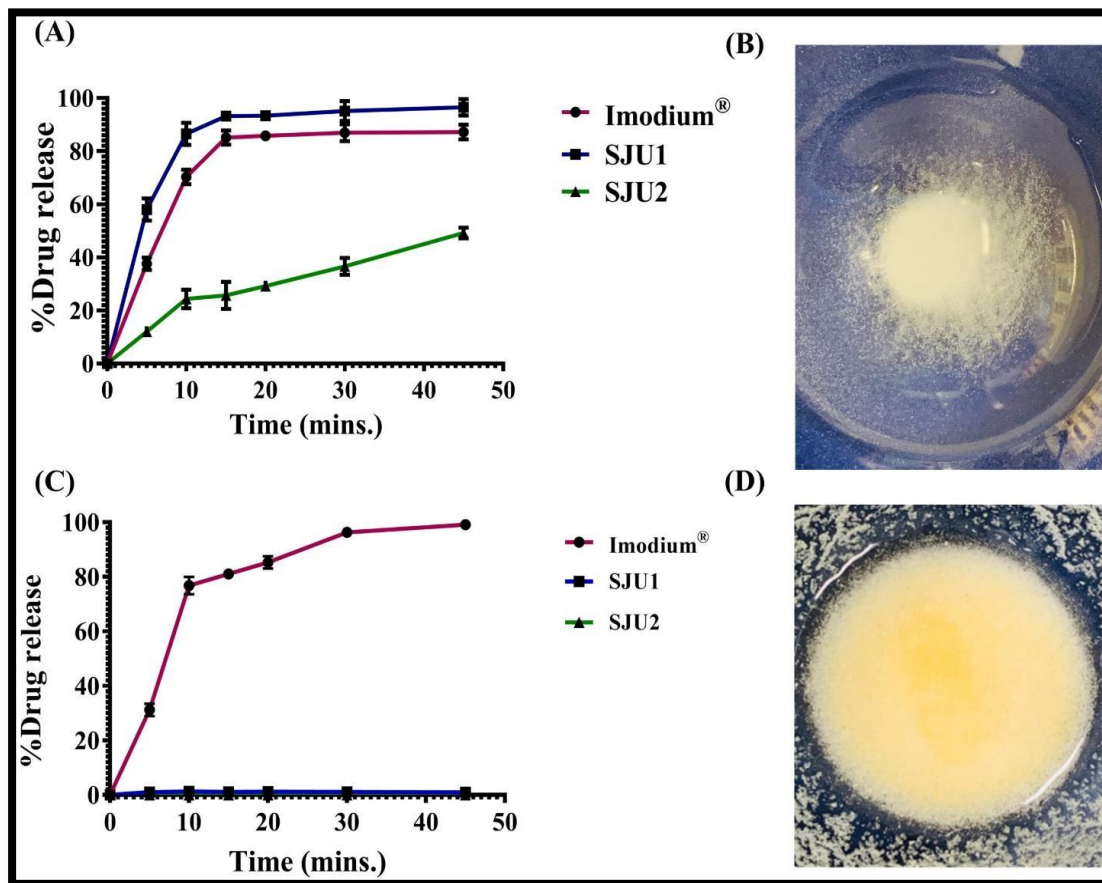


Fig. 28. *In vitro* dissolution studies of Imodium® and SJU1 and SJU2 tablets in 250 mL of FaSSGF (n=3). FaSSGF: Fasted state simulated gastric fluid. A) Single unit dissolution B) Dissolution jar of single unit dissolution (SJU1) C) Multi-unit dissolution (#15 tablets) D) Dissolution jar of multi-unit (#15 tablets) dissolution (SJU1).

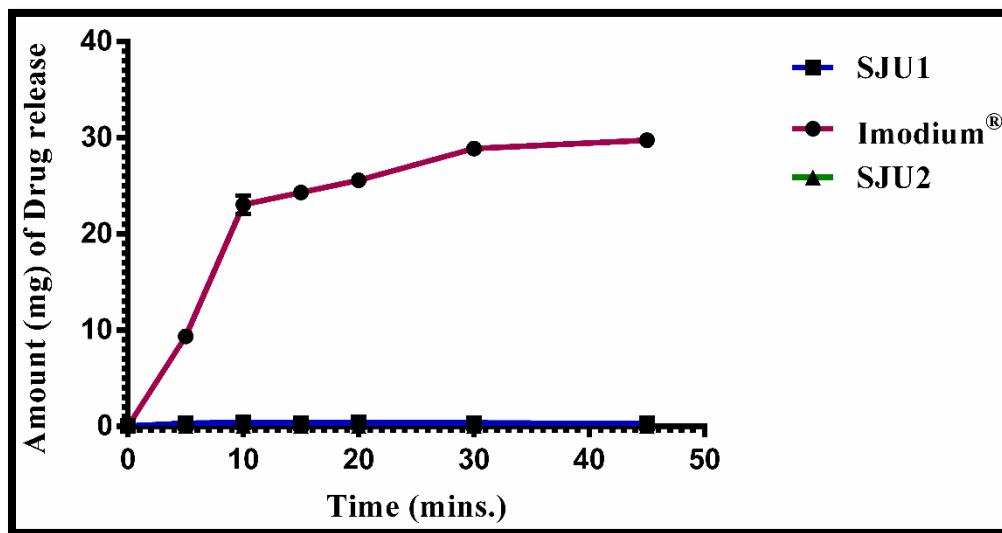


Fig. 29. Amount of drug released in multi-unit (#15 tablets) dissolution. Imodium® exhibited almost complete release of drug (~27 mg), while SJU1 and SJU2 were able to release <1mg throughout the dissolution.

Based on the above data, SJU 1 was able to provide immediate release and negligible release in single and multi-unit (#15 tablets) dissolution respectively. Hence for further studies SJU 1 was employed. From here with SJU 1 will be referred as SJU tablet.

A comparative multi-unit dissolution ($n=3$) was carried out by taking 30 tablets of SJU tablet and Non-SJU tablet (without L-arginine). The dissolution study was carried out in 250 mL of FaSSGF. The pH was monitored continuously for initial 10 minutes. It was observed that >90% of drug was released from Non- SJU tablet, exhibiting no resistance towards drug release. Whereas <5% drug release was noted for SJU tablet, there by indicating ability in resisting the drug release as shown in Fig. 30. This data was in well accordance with the pH vs time plot (Fig. 31), where the pH rose to 8 in dissolution jar of SJU tablet. On the contrary, the pH remained at 2 in the dissolution jar of Non-SJU tablet. 30 tablets of each SJU and Non-SJU tablets before, during and after dissolution were shown in Fig. 32. It was very evident that due to increased pH the LPH loaded filaments from SJU tablets were insoluble during dissolution and settled at the bottom of vessel at end (Fig. 32 A). On the other side in case of Non-SJU tablets the pH remained 2 in dissolution vessel, hence the LPH loaded filaments were solubilized in the vessel (Fig. 32 B).

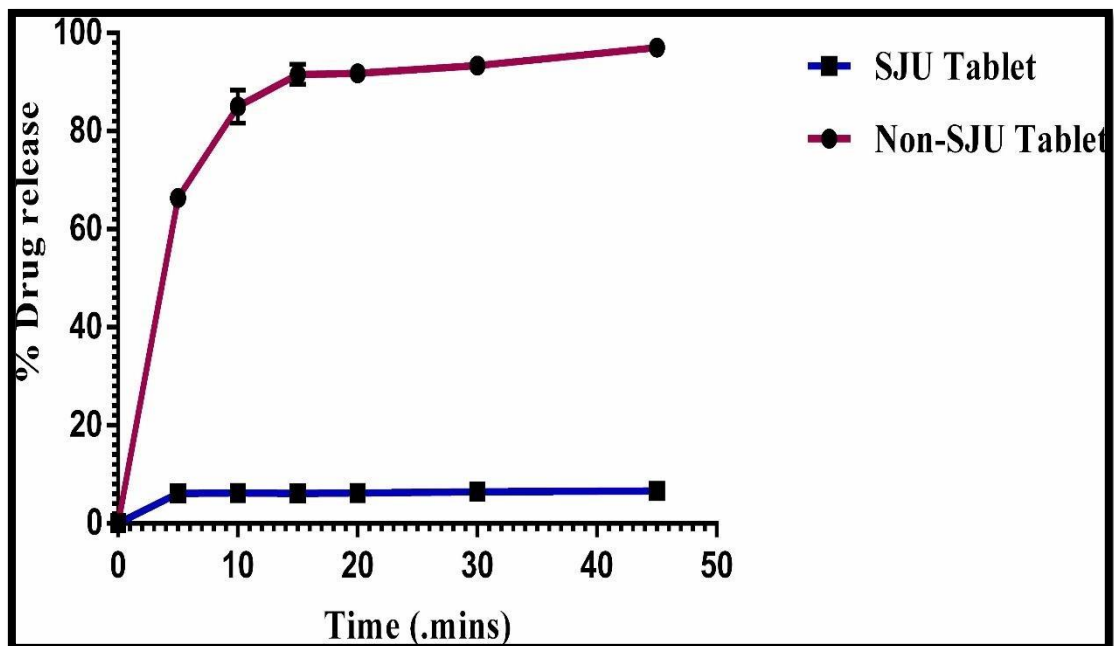


Fig. 30. Multi-unit (#30 tablets) *In vitro* dissolution of SJU tablet and Non SJU tablet in 250 mL of FaSSGF (n=3).

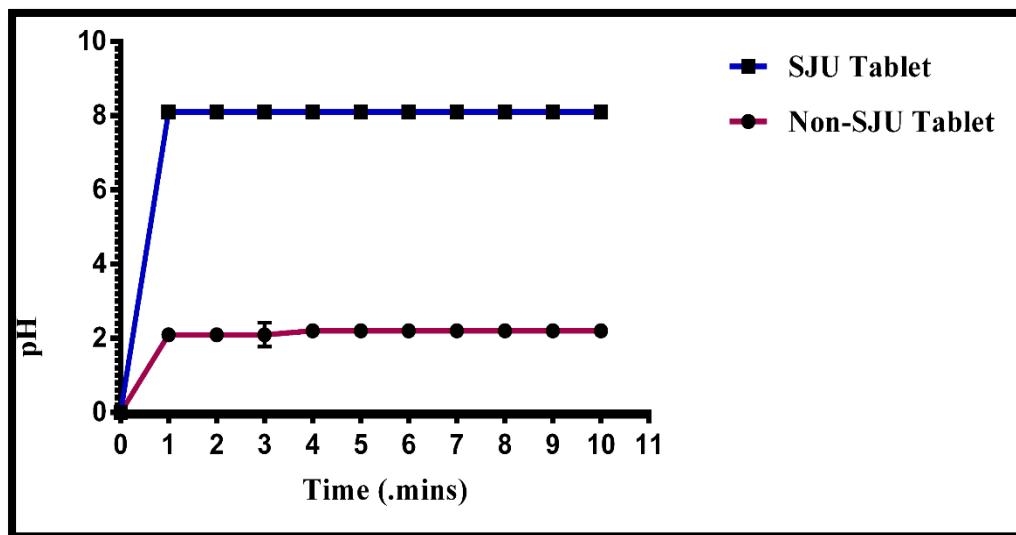


Fig. 31. pH vs time plot.

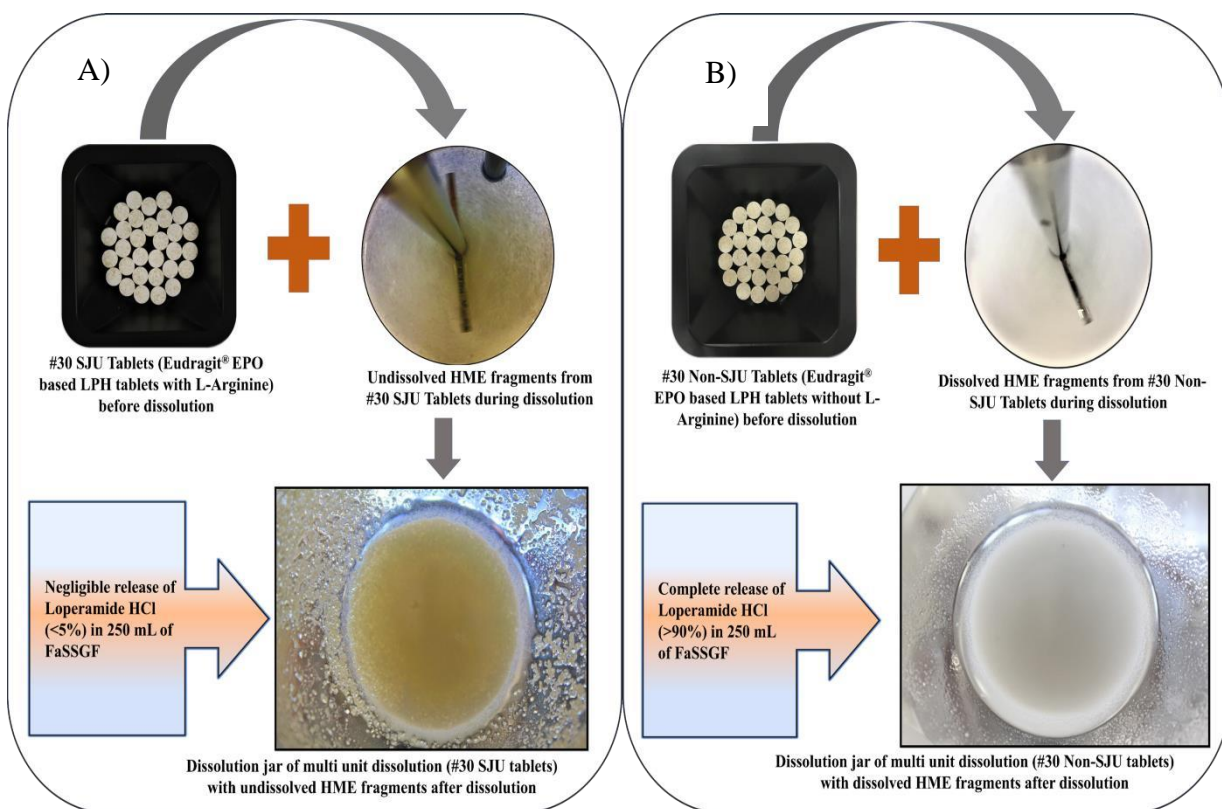


Fig. 32. Multi-unit dissolution (#30 tablets) of A) SJU tablets (before, during and at end of dissolution) and B) Non-SJU tablets (before, during and after dissolution).

Dissolution in Fed state simulated gastric fluid (FeSSGF) was carried out using single unit SJU tablet (n=3) based on Koziolk et al., 2013 and Bou-chacra et al., 2017 (Bou-Chacra et al., 2017; Koziolk et al., 2013). The total study was carried out in three separate conditions i. early stage pH 6.4 ii. Middle stage pH 5 iii. Late stage pH 3 as shown in Fig. 33. The composition of FeSSGF was outlined in Table 18. No drug release was observed in early and middle stages as the pH was ≥ 5 (Fig.33 A and B), where the Eudragit[®] EPO was not soluble. But in case of late stage (pH 3) >90% of drug release was observed (Fig. 33 C) and no traces of filaments were available at the bottom of vessel at end (Fig. 33 D). Our result was accordance with the properties of polymer (insoluble at and above pH 5) mentioned in handbook of pharmaceutical excipients (Raymond et al., 2012).

Table 18: Composition of Fed state simulated gastric fluid
(Adapted from Bou-Chacra et al., 2017; Koziolok et al., 2013)

Ingredient	Early stage	Middle stage	Late stage
Sodium chloride (μM)	148	237.02	122.6
Acetic acid (μM)	-	17.12	-
Sodium acetate (μM)	-	29.75	-
Orthophosphoric acid (μM)	-	-	5.5
Sodium dihydrogen Phosphate (μM)	-	-	32
Milk/Buffer	1:0	1:1	1:3
Hydrochloric acid/Sodium Hydroxide q.s to pH	6.4	5.0	3.0

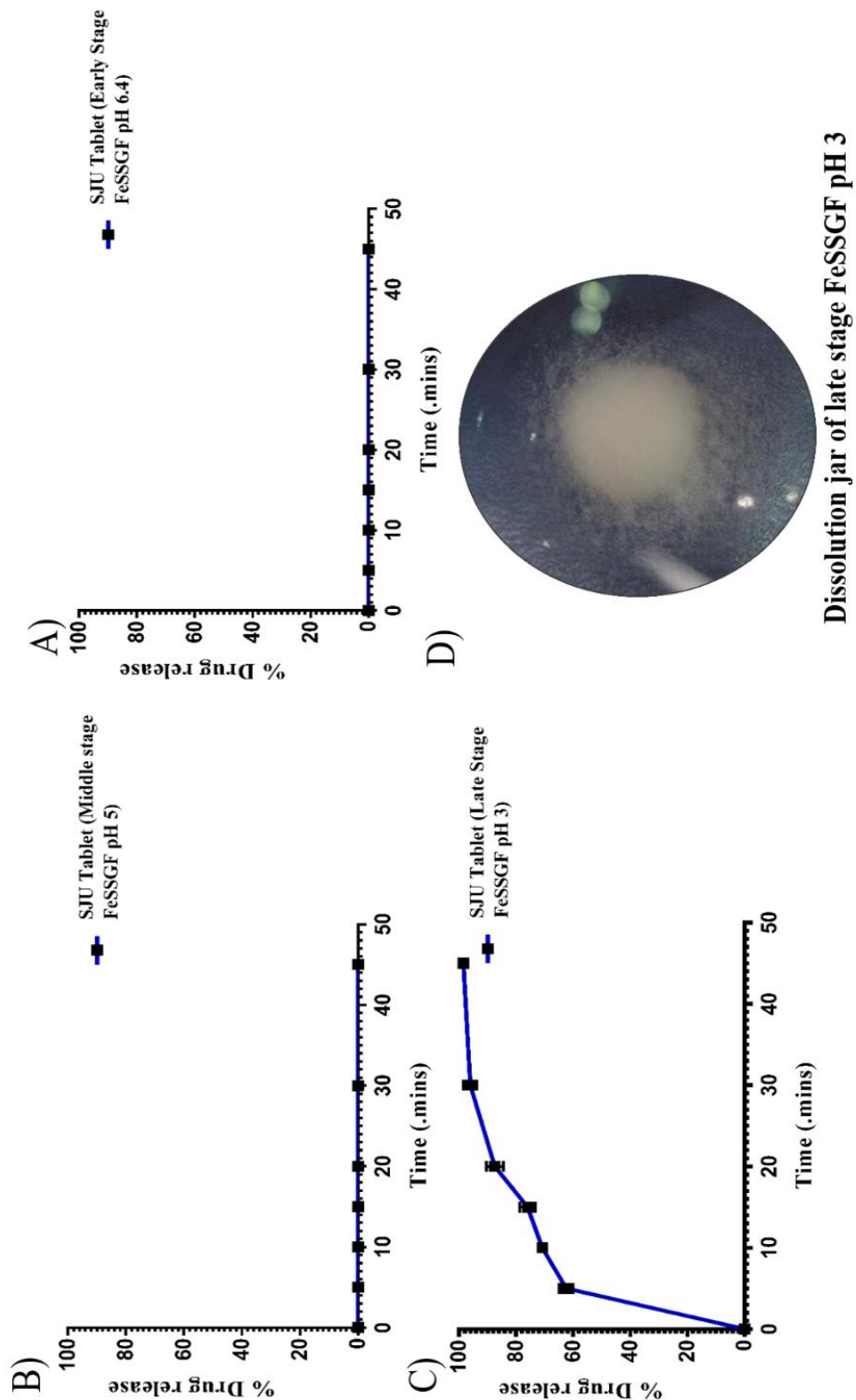


Fig. 33. *In vitro* dissolution of Single unit SJU tablet (n=3) in 500 mL of FeSSGF A) Early stage pH 6.4 B) Middle stage pH 5 C) Late Stage pH 3 D) Dissolution jar of late stage FeSSGF pH 3.

Next, dissolution was carried out for single unit SJU tablet in Fasted state simulated intestinal fluid (FaSSIF) (pH 6.5) and Fed state simulated intestinal fluid (FeSSIF) (pH 5) respectively. The dissolution fluids were prepared based on protocol given by Jogia et al., 2014 (Jogia et al., 2014) and Marques et al., 2004 (Marques, 2004). The composition of FaSSIF and FeSSIF was outlined in Table 19 and Table 20 respectively. It resulted in negligible drug release in both intestinal conditions (Fig. 34A), as the pH was not enough for polymer solubilization and hence there was no release of drug observed. Fig. 34B and Fig. 34C revealed that drug filaments were not solubilized at the end of dissolution. All the dissolution experiments were carried out in triplicate (n=3).

Table 19: Composition of Fasted state simulated intestinal fluid
(Adapted from Jogia et al., 2014) and Marques et al., 2004)

Ingredient	FaSSIF
Sodium taurocholate	3mM
Lecithin	0.75mM
NaOH (Pellets)	0.174g
NaH ₂ PO ₄ .H ₂ O	1.977g
NaCl	3.093g
Purified water q.s	to 500 mL
pH	6.5

Table 20: Composition of Fed state simulated intestinal fluid
(Adapted from Jogia et al., 2014 and Marques et al., 2004)

Ingredient	FeSSIF
Sodium taurocholate	15mM
Lecithin	3.75mM
NaOH (Pellets)	4.04g
Glacial Acetic acid	8.65g
NaCl	11.874g
Purified water q.s	to 1000 mL
pH	5.0

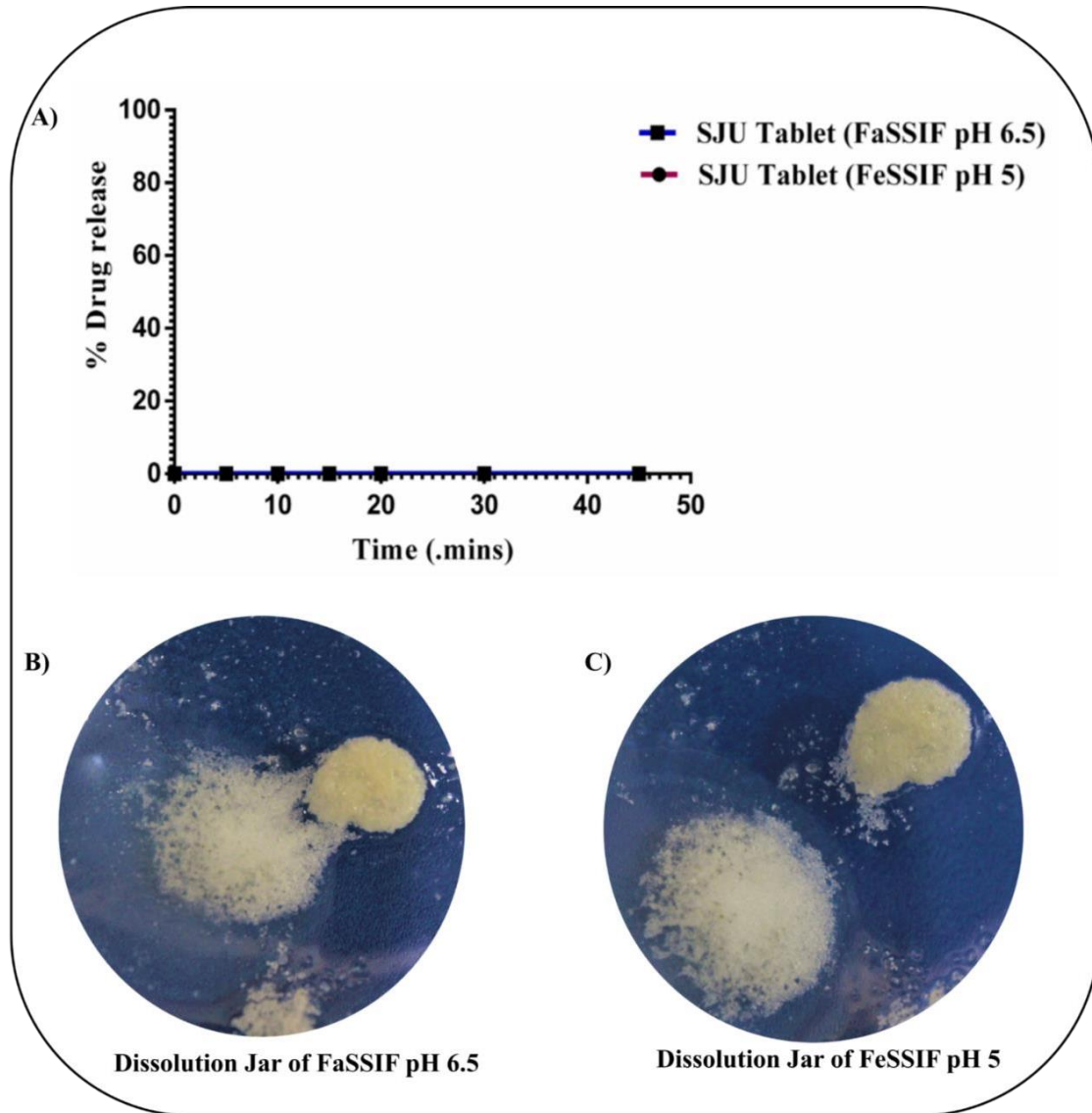


Fig. 34. A) *In vitro* dissolution of Single unit SJU tablet (n=3) in 500 mL of FaSSIF and FeSSIF respectively. B) Dissolution Jar of FaSSIF pH 6.5 C) Dissolution Jar of FeSSIF pH 5.

In vitro step dissolution of single unit SJU tablet (n=3) was carried out as per Solanki et al., 2018 (Solanki et al., 2019). Initial two hours the dissolution was carried out at pH 1.6, after two hours the pH was adjusted to 6.8 followed by collecting the samples up to additional 5 hours. The results showed that >90% of drug release was observed in the initial 2 hours. After the pH shift, only 15% of drug was present in the dissolution jar (Fig. 35A). No traces of filaments were observed in dissolution vessel at the end of initial 2 hours (Fig. 35B). Yet, once the pH has been shifted then rapid precipitation of drug and polymer was noted (Fig. 35C). Our observation was in well accordance with the literature (Wei et al., 2016).

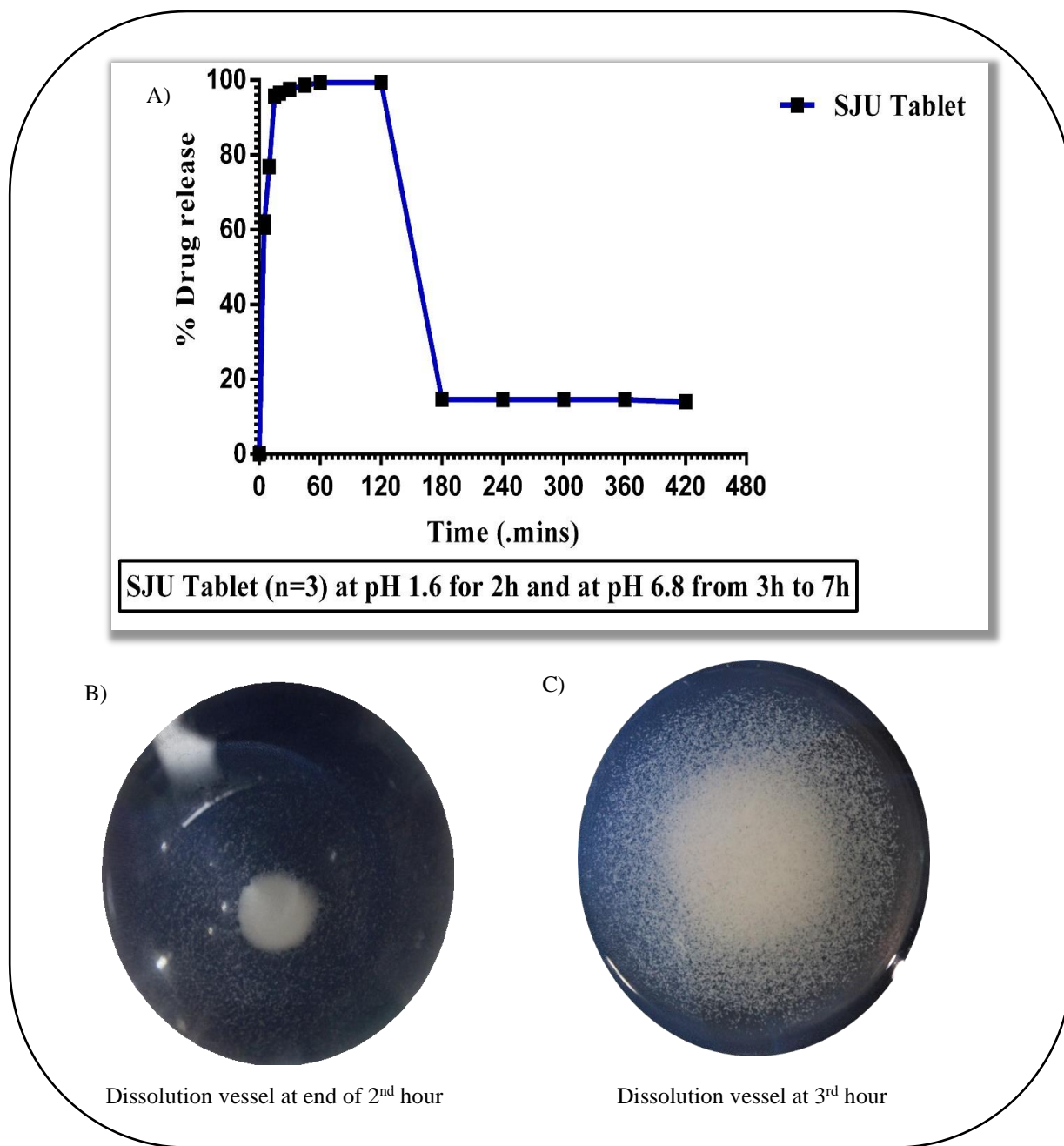


Fig. 35. A) *In vitro* step dissolution of Single unit SJU tablet (n=3) at pH 1.6 for initial 2 hours followed by additional 5 hours after changing pH to 6.8. B) Dissolution vessel at end of 2nd hour C) Dissolution vessel at 3rd hour (After pH shift to 6.8).

Pharmacologic effect of loperamide is attained primarily by binding peripherally as a μ -receptor agonist on the mesenteric plexi of enteric wall. To evaluate the significance of HME processing technique in resisting the drug release during multi dose oral ingestion. A comparative dissolution study was conducted at pH 6.8 for one hour. All the samples were tested in triplicate ($n=3$). Within this study amount of drug release was compared between 60 mg of pure API and crushed filaments (based on Eudragit[®] EPO) having equivalent amount of 60 mg of drug. Pure API was used in this study instead of marketed formulation Imodium[®] comprising lactose, cornstarch, talc, and magnesium stearate. Because the pharmacologic effect is purely dependent on active form of drug available at the site of action. At the end of dissolution, a maximum of $18\% \pm 0.5$ and $3.5\% \pm 0.5$ was released from pure API and filaments respectively as shown in Fig. 36. The lower drug release from filaments can be attributed to its insolubility at pH 6.8 as Eudragit[®] EPO is not soluble at $pH > 5$. This test was to prove that HME was imperative in preparation of LPH ADF which aids in producing molecular dispersion of drug within carrier polymer. Hence during dissolution, it was very essential for the initial solubilization of carrier polymer for the release of drug.

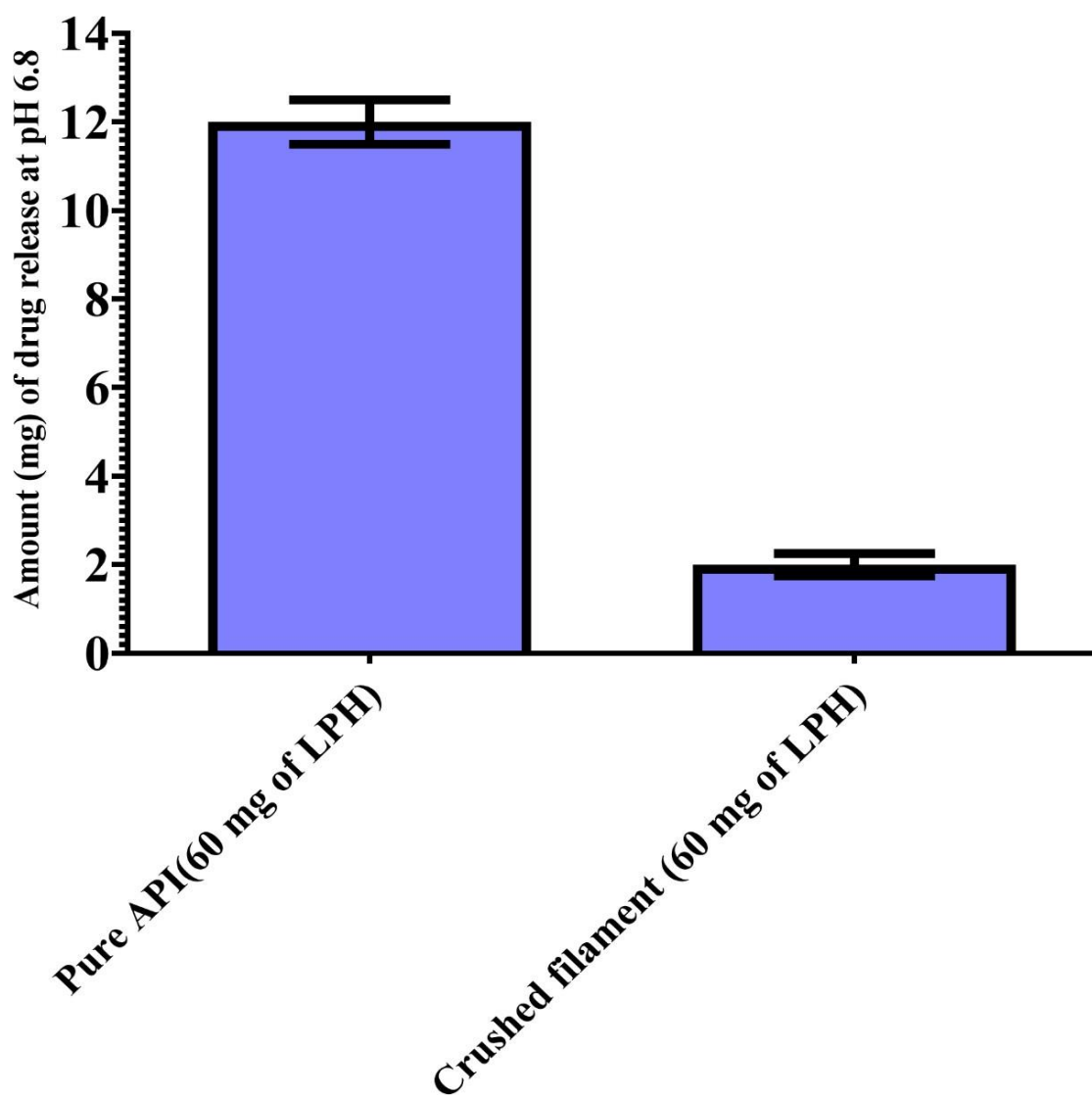


Fig. 36. Amount of drug released (~mg) at pH 6.8 during one hour between Pure API (60 mg) and Crushed filament with an equivalent amount of 60 mg (n=3).

Eudragit® EPO is a copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate (2:1:1). Eudragit® EPO is soluble in a pH range of 1-4 and no reported solubility was found above pH 5 (Huang et al., 2015). Eudragit® EPO is an amorphous polymer and cationic in nature. Literature indicated its application in enhancement of solubility of poorly soluble drugs (Saal et al., 2017). LPH reported to have a very low solubility (BCS class IV drug). During extrusion of LPH with Eudragit® EPO (low T_g 52°C), it required a modified screw design (low shear type) to obtain drug loaded filaments. Subsequently, another gastric soluble polymer Kollicoat® Smartseal 100P (novel functional polymer from BASF) was investigated. It is a cationic polymer based on methyl methacrylate and diethylaminoethyl methacrylate copolymer. Kollicoat® Smartseal 100P is reported to be soluble at pH<5 and insoluble at neutral pH (BASF, 2019). It's a reverse enteric polymer used for taste masking and moisture protection. Similar to Eudragit® EPO low shear screw design was utilized for extrusion with Kollicoat® Smartseal 100P (low T_g 50°C).

In single unit dissolution of SJU1 and SJU2, the pH remained constant (~1.6) during dissolution. pH of medium was found to be unaltered by the presence of 100 mg of L-arginine per tablet. SJU1 was able to provide complete drug release compared to SJU2, which exhibited a slower release. Cationic polymeric backbone was able to solubilize quickly, thus getting LPH faster into solution in case of Eudragit® EPO (LPH was solubilized within polymer). Hence, SJU1 appears to provide rapid release on par with commercial product Imodium®. Despite having similar cationic polymeric backbone in Kollicoat® Smartseal 100P, interestingly SJU2 was able to achieve only a release of 50% in 45 minutes. Kollicoat® Smartseal 100P has diethyl group instead of dimethyl group in Eudragit® EPO, moreover Kollicoat® Smartseal 100P is more lipophilic in nature. Slower dissolution of Kollicoat® Smartseal 100P is attributed to i) diethyl group which is bulkier and more hydrophobic than dimethyl group ii) more lipophilic nature. Thereafter, in multi-unit dissolution, the rise in pH was noted to be 8.67. Hence, the tablets SJU1 and SJU2 prepared using SJU technology were remained undissolved in dissolution vessels. It was obvious that cationic polymeric backbone found to be insoluble in higher pH. Because of this phenomenon, the drug release from SJU1 and SJU2 was found to be negligible (<1mg) throughout dissolution. At the same

time, Imodium[®] (comprising Lactose, cornstarch, talc, and magnesium stearate) showed almost complete release of drug.

USFDA made an announcement on June 7th, 2016 to encourage a safer use of Imodium[®] (USFDA, 2018b). High doses of oral ingestion of Imodium[®] (poor man's methadone) will lead adverse cardiac events. Accordingly, to confront the growth of opioid agonist drugs like Imodium[®], we developed SJU technology approach. LPH loaded filaments of an acid soluble polymer - Eudragit[®] EPO was prepared using hot melt extrusion. Filaments were crushed and converted into a tablet containing 100 mg L-arginine. In single unit dissolution Imodium[®] and SJU1 exhibited >85% of release in 15 minutes with no presence of filaments observed in SJU1 dissolution jar. In multi-unit dissolution SJU1 and SJU2 demonstrated negligible release contrary Imodium[®] which exhibited >90% of release in 30 minutes. The success of our technology was exemplified by SJU1 that fulfilled the purpose of serving immediate release in single unit dissolution in addition to resisting the drug release in multi-unit dissolution. According to previous literature, abuser consumes 30 or higher tablets to get euphoria. We designed SJU1 tablets to deter the abuse in 15 tablets itself. In present work L-arginine a basic amino acid was employed throughout the study. It will be interesting to evaluate the other basic amino acids like lysine, histidine for similar application.

6. Limitations

Based on the USFDA an abuse deterrent formulation is not abuse proof or tamper resistant. The main objective at end is to deliver the drug to the patient. Hence there might be abuse of these products as well. Therefore, in present work.

- ✚ Although majority of studies suggested by the USFDA were performed, few of the elements such as large volume extraction, heating-cooling cycle, and insufflation characterizations were not carried out due to limited scope and resource constrain.
- ✚ Drug extraction from crushed egglets was not carried out. The drug extraction may be high from grounded egglets.
- ✚ Multi tablet (egglet) solvent extraction may be possible and can be abused through IV route.
- ✚ SJU tablet containing loperamide should be administered on an empty stomach to achieve immediate release for diarrheic patients.
- ✚ Multi dose oral ingestion of SJU tablets may be possible with co-administration of apple cider vinegar (pH 2-3).

7. Summary

Abuse Deterrent Immediate Release Egg-Shaped Tablet Using 3D Printing

Technology: Quality by Design to Optimize Drug Release and Extraction.

As per our published work (Nukala et al., 2019b)

- ✚ An egg-shaped immediate release abuse deterrent formulation (egglet) was successfully developed using a fused deposition modeling (FDM) 3D printing technology and hot melt extrusion.
- ✚ PVA (Poly vinyl Alcohol) with 10% w/w sorbitol was found be the most suitable material for the preparation of crush and drug extraction resistant egg-shaped tablets (egglets).
- ✚ Optimized egglets passed most tests described in the USFDA guidance for abuse deterrent opioids. Hardness (> 500 N) and physical manipulation (80% of particles more than > 1 mm size) confirmed the snort-resistant potential of egglets.
- ✚ Egglets prepared using polymeric filaments of 15% w/w drug load and 45% infill density in small dimension (X-6.00mm: Y-4.4mm: Z-3.3 mm) were

meeting the QTPP—D85 < 30 min and percentage drug extraction in small volume of water < 15%.

✚ The optimized response models for dependent variables also correlated well with the data generated, confirming its validity.

✚ Thus, hot melt extrusion coupled with FDM 3D printing offers a platform for the preparation of dosage forms of opioids with an abuse deterrent property.

Development of Multi-dose Oral Abuse Deterrent Formulation of Loperamide Using HME.

As per our published work (Nukala et al., 2019a).

✚ Modern day abusers have been actively moving towards easily accessible OTC drugs like loperamide for attaining a ‘high’. To deter the administration of LPH in toxic and life-threatening conditions, the present study reports the successful development of a formulation for multi-dose oral abuse.

✚ Molecular dispersion of LPH in gastric soluble polymers (Eudragit® EPO and Kollicoat® Smartseal 100P) was achieved with hot melt extrusion.

✚ A combination of these filaments with a free base like L-arginine proved to be useful for deterring multi dose oral drug abuse.

✚ Drug release from SJU1 (Eudragit[®] EPO based) tablets and Imodium[®] (marketed formulation of Loperamide) had a similar dissolution profile for single unit dissolution. Most importantly, SJU1 tablets exhibited minimal drug release in multi-unit dissolution due to increase in pH to 8, where Eudragit[®] EPO is insoluble.

✚ Hence, SJU formulation technology (LPH loaded Eudragit[®] EPO filament and L-arginine) could be an ideal, safe and promising technology to deter multi-dose oral ingestion abuse for loperamide.

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